



Synergistic Activation of Doxorubicin against Cancer: A Review

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Abstract

Doxorubicin is an anthracycline drug extracted from *Streptomyces peucetius* and used in the treatment of several cancers including breast, lung and ovarian cancers. A major limitation for the use of doxorubicin is cardiotoxicity, patients need to more possible to achieve efficacy at lower doses with lesser toxicity for this phytochemicals which occur in many vegetables, plants and fruits frequently consumed by humans, it shows antimicrobial and anticancer activity. These findings suggest that doxorubicin and phytochemicals combination may be most effective in cancer chemo preventative therapy.

Introduction

Cancer is a proliferative disorder which involves deregulation of multiple signaling pathways, apoptosis, proliferation, angiogenesis and metastasis [1]. Globally, it is estimated that almost 1.7 million new cases of cancer will be diagnosed in 2017. Among females, breast (30%), lung (12%) and colorectal (8%) cancers are the most common. Prostate cancer is the most common cancer among males (19%), followed by lung (14%) and colorectal (9%) cancers [2,3,4]. Cancer is the second most common disease after cardiovascular disease and it accounts for about 7 % in India and 23% death in USA per year. Among women the highest numbers of deaths are caused by cancer of mouth, stomach, breast, colon, rectum and cervix. While among men, cancers of lung, mouth, prostate, liver, colon has resulted in highest mortality [5,6]. Cancer may be caused by various factors. For example, external factors like tobacco, radiation, chemicals and internal factors like mutations, hormones, immune condition, environmental changes and life style changes may contribute to cancer development [1]. Many chemical compounds present in the air, industrial water, contaminated food and other synthetic compounds may act as carcinogens [1,6].

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Received Date: 20 Feb 2018

Accepted Date: 28 Mar 2018

Published Date: 04 Apr 2018

Citation:

Wakharde AA, Awad AH, Bhagat A, Karuppaiyl SM. Synergistic Activation of Doxorubicin against Cancer: A Review. *Am J Clin Microbiol Antimicrob*. 2018; 1(2): 1009.

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Doxorubicin

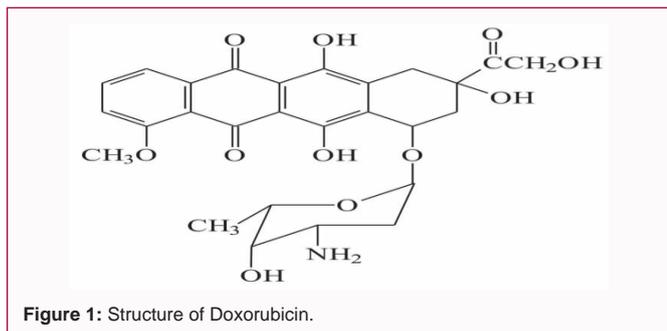
Doxorubicin is a broad spectrum antitumor antibiotic [7]. Among the available cancer drugs, doxorubicin (Adriamycin) is considered as one of the most effective [8]. Doxorubicin was isolated from *Streptomyces* species and is widely used as an anticancer agent [9]. Doxorubicin a member of the anthracycline group of compounds with a four member ring system containing a chromophore, anthraquinone and aminoglycoside has been an important agent since 1974 [9]. It was first used in clinical trials in the 1960's and still it is a frontline chemotherapeutic agent [10]. Doxorubicin shows very low oral bioavailability, low permeability and acute toxicity to normal tissue [11]. It under goes acid hydrolysis in stomach and is susceptible to cytochrome P450. It is available in the market as injectables namely Adriamycin, Rubex and Doxil etc. [12]. It exhibits Fluorescence with excitation maximum of 480 nm and emission maximum at 600 nm [13](Figure 1).

Target of doxorubicin

Doxorubicin acts on cancer cells through intercalation into DNA resulting in the inhibition of DNA synthesis and function. It inhibits transcription through inhibition of DNA-dependent RNA polymerase [14]. Doxorubicin is a DNA topoisomerase II inhibitor, DNA intercalator leading to DNA strand breaks and formation of Reactive Oxygen Species (ROS) in cells [15]. It forms a cleavable complex with DNA and DNA topoisomerases II leading to eventual DNA breaks [16].

For better therapeutic effectiveness, often combination anticancer drugs are used [17]. All cancer therapies target to kill cancer cells and not to damage normal cells, Angiogenesis blockers, biotherapies, monoclonal antibodies, bone marrow transplants, cryosurgery, chemotherapy, laser therapy, photodynamic therapy and radiotherapy are widely used [14,17].

To improve therapy regimen with doxorubicin, it is necessary to evaluate a tumor specific



doxorubicin based combination therapies targeting cellular pathways [18](Table 1 and 2). Dubois and Mosteller’s formula $BSA(\text{Body Surface Area}) (M^2) = ht (cm) \times wt (kg)$ divided by 3,600, and then take the square root of the answer.

Side effects of doxorubicin

The common side effects of Doxorubicin include nausea, vomiting, alopecia, bone marrow suppression, cardio toxicity, immune suppression, nephrotoxicity, unusual tiredness, weakness and red coloration of urine [19]. Prolonged use of doxorubicin can cause severe heart damage, even years after the patient has stopped taking doxorubicin. The risk of heart damage after stopping doxorubicin is found in children. Some rare effects are black tarry stools, pinpoint red spots on skin and unusual bleeding [20].

Doxorubicin and Cisplatin

Cisplatin (Cis-diammine dichloro platinum) is platinum based frequently used for treatment is effective against various types of cancers, including lymphomas, and sarcomas, germ cell tumors, carcinomas. Mechanism involves linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms causing DNA damage, and consequently inducing apoptosis in cancer cells [49]. Cisplatin combination chemotherapy is the base treatment of various cancers. Cisplatin sensitivity is high but many cancer patients and it will ultimately relapse with cisplatin-resistant disease. Multidrug resistance of cisplatin include changes in cellular uptake and efflux of cisplatin, activation coordinately regulated biotransformation and detoxifying system in the liver, and increase in DNA repair and anti-apoptotic mechanisms [50]. For overcome the cisplatin drug resistance, commonly used in combination with other drugs in treating breast, colon, lung, prostate, melanoma and cervical cancer. Cyclophosphamide, doxorubicin and cisplatin combination chemotherapy were treated for advanced carcinomas of salivary gland origin showed encourage results [51]. The combination of doxorubicin and cisplatin is effective. It might be considered suggestive patients with diffuse malignant pleural mesothelioma DMPM [52]. The combination of doxorubicin and cisplatin has been shown to be of significant in treating gynecological malignancies and endometrial adenocarcinoma. The response rate produced is significantly higher with this combination regimen [53]. Doxorubicin in combination with cisplatin is synergistically effective against breast cancer cell lines with enhanced by combined treatment with the small molecule DNA-PK inhibitor [54].

Doxorubicin and Decursin

Anti-tumor activities of decursin isolated from the roots of *Angelica gigas* has been used in traditional oriental medicine [31]. Decursin revealed the anticancer effects on apoptosis induction and

Table 1: Dosage of Doxorubicin.

Sr.no.	Cancer Types	Dosage of Doxorubicin Used
1	Leukaemia	75mg/m ² -90 mg/m ² (2.4mg/kg)
2	Soft Tissue Sarcoma	40mg/m ² -60 mg/m ²
3	Hodgkin’s Lymphoma	40mg/m ² -60 mg/m ²
4	Bladder Cancer	40mg/m ² -60 mg/m ²
5	Stomach Cancer	40mg/m ² -60 mg/m ²
6	Lungs Cancer	40mg/m ² -60 mg/m ²
7	Ovarian Cancer	40mg/m ² -60 mg/m ²
8	Thyroid Cancer	40mg/m ² -60 mg/m ²
9	Multiple Myeloma	9mg/m ²
10	Breast Cancer	40mg/m ² -60 mg/m ²
11	Neuroblastoma	40mg/m ² -60 mg/m ²
12	Wilm’s Tumour	40mg/m ² -60 mg/m ²
13	ALL	40mg/m ² -60 mg/m ²
14	Osteosarcoma	40mg/m ² -60 mg/m ²
15	AML	40mg/m ² -60 mg/m ²

inhibition of cell growth in several cancer cell lines. However, the molecular mechanism by which decursin inhibits cell proliferation and cell apoptosis [36]. Decursin exerted antitumor activity by apoptosis induction or angiogenesis inhibition in various cancers including colon, prostate, bladder and leukemia. Combined decursin and doxorubicin significantly induced apoptosis via the inhibition of mTOR and STAT3 signaling pathway in multiple myeloma cells. Notably, the found synergism of decursin, this combination may be significant for multiple myeloma patients [36,53].

Doxorubicin and Docetaxel

Docetaxel is a semi-synthetic taxane analog, from the European yew (*Taxus baccata*).

Taxane class of chemo therapeutic drugs posses confirmed therapeutic efficacy in ovarian, lung, breast, cancers [55]. The mechanism of docetaxel is the inhibition microtubule depolymerisation that causes aberrant mitosis and often leads to cell death. Additionally, docetaxel may evoke oxidative stress, however, potentiating cardio toxicity [56,57]. Combination of doxorubicin and docetaxel is clinically effective against cancers. Combination therapy with these drugs has been proven particularly effective in the treatment of breast cancer. Combined Doxorubicin and docetaxel chemotherapy generated oxidative damage to plasma proteins [58]. Synergistic effect of the Docetaxel and doxorubicin combination on metastatic prostate cancer cells derived from the bone (PC3) and brain (DU145) is reported *in vivo* [26].

Doxorubicin and Curcumin

Curcumin, a phenolic compound obtained from the rhizome of *Curcuma longa* L., has a wide spectrum of biological and pharmacological activities. It has been used for thousands of years as a healing agent for a variety of diseases. Curcumin has been shown to exhibit anticancer, anti-oxidant, anti-arthritis, anti-amyloid and anti-inflammatory properties. The natural therapeutic properties are show up in its regulation of signal transduction including NF-κB, Akt, MAPK, p53, Nrf2, Notch-1, JAK/STAT, β-catenin, and AMPK and inflammatory pathway, cell cycle arrest induction, and apoptotic features. PEG-DOX-Cur NPs enhanced antitumor activity

Table 2: Efficacy of Doxorubicin drug combinations.

Sr No	Drug Combination	Clinical Uses	Study	References	Output
1	Doxorubicin + Verapamil	Metastatic breast cancer	<i>In vivo</i> (4T1-R cells in mice)	[21]	Synergistic
2	Doxorubicin + Resveratrol	Leukemia	Cell lines (AML)	[22]	Synergistic
3	Doxorubicin + Gemcitabine	Prostate & Various Cancers	<i>In vitro</i> (AT1 rat prostate carcinoma cells)	[23]	Synergistic
4	Doxorubicin + Docetaxel	Prostate cancer	<i>In vitro</i>	[24]	Synergistic
5	Doxorubicin + Gemtirinib	Prostate & Breast Cancers	<i>In vivo</i>	[25,26]	Synergistic
6	Doxorubicin + Zoledronic acid	Prostate and breast cancer	Cell lines (prostate 22Rv1 & PC3, breast MDA-MB-231)	[27,28]	Synergistic
7	Doxorubicin + Paclitaxel	Breast Cancers	<i>In vivo</i> (HepG2 and Huh7 <i>in vitro</i> and murine H22-BALB/c mice <i>in vivo</i>)	[29]	Synergistic
8	Doxorubicin+Cyclophosphamide	Breast Cancer	Cell lines	[17]	Synergistic
9	Doxorubicin + Quercetin	Breast cancer cells	Cell Lines (MCF-10A)	[18]	Synergistic
10	Doxorubicin + Flurouracil	Metastatic breast cancer	<i>In vitro</i>	[17]	Synergistic
11	Doxorubicin + TGFβInhibitor	Breast Cancer	<i>In vivo</i> (4T1 breast cancer cells)	[30]	Synergistic
12	Doxorubicin + Decursin	Multiple myeloma cells	Cell Lines (U266 cells)	[31]	Synergistic
13	Doxorubicin + Vincristine	Ewings Sarcoma cells	<i>In vitro</i>	[32]	Synergistic
14	Doxorubicin + Lavastatin	Ovarian Cancer	Cell Lines (A2780 cells)	[33]	Synergistic
15	Doxorubicin/ Paclitaxel + Silymarin	Colon Cancer	Cell Lines (LoVo Cells)	[34]	Synergistic
16	Doxorubicin + Lavastatin	Colon cancer	<i>In Vitro</i> (B16F10, B78, A-375 and Hs 294T melanoma cells <i>in vitro</i>)	[35]	Synergistic
17	Doxorubicin + Combretastatin	Lungs Carcino Melanoma	<i>In vivo</i>	[36]	Synergistic
18	Doxorubicin + Paclitaxel	Heptocellular carcinoma	<i>In vitro/ vivo</i> (HepG2 and Huh7 <i>in vitro</i> and BALB/c mice <i>in vivo</i> .)	[29]	Synergistic
19	Doxorubicin + melanotonin	Hepatocellular Carcinoma	Cell lines (HepG2 and Bel-7402)	[37]	Synergistic
20	Doxorubicin + Valproic acid	Haepatocellular carcinoma	Cell Lines (HepG2 cells)	[38]	Synergistic
21	Doxorubicin + Cisplatin	Osteosarcoma	<i>In vivo</i>	[39,40]	Synergistic
22	Doxorubicin + Gallic acid	Adenocarcinoma	Cell lines	[41]	Synergistic
23	Doxorubicin + Cyclosporin –A	Various Cancers	<i>In vitro</i>	[42]	Synergistic
24	Doxorubicin/ Etoposide + Salinomycin	Various Cancer	Cell Lines	[43]	Synergistic
25	Doxorubicin + Docetaxel	Various Cancer	<i>In vitro</i> (PC3 and DU145)	[44]	Synergistic
26	Doxorubicin + Carboplatin	Various Cancer	<i>In vitro</i>	[45]	Synergistic
27	Doxorubicin + Curcumin	Various Cancers	<i>In vitro</i> (A549 cells)	[46]	Synergistic
28	Doxorubicin + Etoposide	Various Cancers	<i>In vivo</i>	[47]	Synergistic
29	Doxorubicin + Genistein	Tumor cell	Cell Lines	[48]	Synergistic
30	Doxorubicin + Simvastatin	Cancer cells	Cell lines	[7]	Synergistic

using xenograft mice with hepatic tumors. Anti-tumor activities of Doxorubicin-Curcumin *in vitro* against A549 cells were then evaluated and compared with that of free Doxorubicin. Cytotoxicity evaluation showed that DOX-CUR-LCLs exhibited a significantly higher antitumor activity than other DOX preparations. These results suggest that novel DOX-CUR-LCLs, combination of DOX and CUR administered in long-circulating liposomes could improve antitumor activity [46].

Doxorubicin and Gemtirinib

Gamitirinib, mitochondrial-stress inducer is to develop different stress pathways in cancer therapy. Doxorubicin and Gamitirinib combination synergistically enhanced cancer-specific cytotoxic activity throughout stimulation of CHOP and JNK signalling pathways and activation of the proapoptotic protein without aggravating cardiotoxicity [61]. The drug combination dramatically increased caspase activity and concomitant cell death in 22Rv1 and MDA-MB-231 cells.

Doxorubicin and Paclitaxel

Paclitaxel is a tubulin inhibitor isolated from the bark of *Taxus brevifolia* (Pacific Yew Tree) [59]. The combination of doxorubicin and paclitaxel is highly active against breast cancer. Heptocarcinoma cancer is most common solid tumor in worldwide. This combination showed promise in the treatment of hepatocarcinoma cancer also well as breast cancer. It showed synergistic activity in two HCC cell lines HEPG2 and Huh7 *in vitro* and *in vivo* in mice [60].

Doxorubicin and Zolendronic Acid

Zolendronic acid is a potent, nitrogen containing bisphosphate. Bisphosphate is a group of stable synthetic analogues of pyrophosphate that possess strong affinity for bones [61]. They can be separated in two groups, the nitrogen containing bisphosphate and non-nitrogen bisphosphate [62]. This combination synergistically induced apoptosis in breast and prostate cancer [14,27,63]. *In vivo* it elevated level of apoptosis in both androgen sensitive and insensitive prostate cancer. It is also effective in lung cancer, leukemia, soft tissue

sarcoma and different types of carcinoma [26]. These combination increased anti-tumor effect is generated when doxorubicin and zoledronic acid are given in sequence in both hormone-sensitive and insensitive prostate cancer cells *in vitro* [64].

Doxorubicin and Quercetin

Quercetin is a plant based flavonoid. Other flavonoids are rutin and tangeritin, naringin, hesperidin [18]. Rutin is the most common flavonoid containing the quercetin present in the diet which shows, anti-inflammatory, antioxidant and anticancer properties e.g. cell cycle regulation, inhibition of tumor necrosis [65]. This combination synergistically effective *in vitro* murine model against breast cancer MCF-7 cells [18,65]. Doxorubicin with Quercetin may be effective for chemotherapy of human breast cancer, and probably of other cancers based on doxorubicin. It can reduce the side effects of doxorubicin in non-tumoral cells [18]. Quercetin potentiated the antitumor effects of Doxorubicin on liver cancer cells. The development of Quercetin may be useful in a combination treatment with Doxorubicin for enhanced therapeutic efficiency against liver cancer [46,66].

Doxorubicin and Genistein

Genistein (4,5,7-trihydroxyisoflavone) is an isoflavone present in soya. It has a heterocyclic diphenolic structure similar to estrogen. Genistein regulate numerous signaling pathways in cancer cells and promote cancer cell death [66]. Genistein has antioxidant and weak estrogen effect, cell proliferation and transformation activity. This combinational *in vitro* study is promoting the effect on breast cancer. It reduced genotoxicity induced by androgenic steroids, risk of some hormone related breast and prostate cancers. Genistein combined with doxorubicin exhibited a synergistic effect on MCF-7 cells, and genistein reduced the chemoresistance of these cells.

Doxorubicin and Lovastatin

Lovastatin exhibits antiproliferative activity against cancer cells without causing damage to normal cells. Combination study with lovastatin and doxorubicin revealed synergistic interaction exhibited of anti tumor effect on both murine and melanoma cells. Lovastatin may increase the efficiency of chemotherapeutic agents in the treatment of malignant melanomas lovastatin synergizes with doxorubicin and induces of ovarian P53 cancer cells, a chemotherapeutic combination used to treat of ovarian cancer [43].

Doxorubicin and Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized in pineal gland it regulates the huge amount of changes of with a physiological functions such as the regulation of the light and dark sleep cycle and the circadian rhythm. In addition, melatonin also has biological functions, including a cytoprotective role and immunomodulatory effect. Melatonin regulates antioxidative processes and is directly involved in the prevention of tumor, promotion, progression in different cancers [66]. The synergism of Melatonin and Doxorubicin inhibited the cell growth and induced cell apoptosis in human hepatoma cell lines HepG2 and Bel-7402.

Challenges to Chemotherapy

In cancer therapy drug resistance is a major obstacle. Resistance to drugs continues to be a major problem in oncology affecting the majority of cancer patients. Cells become resistant to various drug through various mechanisms the modification of drug targets, alteration in drug metabolism and genetic changes of cells to targeted

pathways. A better perceptive of oncogene networks like to improve therapeutic strategies by identifying optimal combinations based on the genetic lesions in the tumors. Significantly, tumors are highly heterogeneous and this may well substantially contribute to primary or acquired resistance.

Why the Combination is Important

There are several limitations regarding systemic administration of single-drug chemotherapy, including poor bioavailability and multidrug resistance. In addition, drug accumulation at the tumor sites is often too low to reach an effective dose, requiring high drug dose during administration which can cause severe adverse side effects. Single drug chemotherapies may not be effective enough to suppress all cancer cell growth given the homogeneous distribution of cancer cells within the tumors. Combination chemotherapy of multiple anticancer drugs has been extensively developed since it can reduce multidrug resistance and side effects as a result of lower dosage of each drug, which may result in more efficient tumor responses. However, it remains challenging to obtain significant antitumor effect with reduced normal tissue toxicity of different drugs possess different physical and chemical properties.

Importance

Combination chemotherapy is emerging as an important strategy for better long term prognosis with decreased side effects and increased therapeutic effectiveness. Doxorubicin is a commonly used chemotherapeutic drug to treat different cancers. Drug combination is mostly used in treating dreadful diseases like AIDS, cancer. Some of these combinations improved the effectiveness in cytotoxicity, several helped to prevent side effects by reducing dose, and some combinations helped in overcoming drug resistance. It is an effective in fighting tumor growth and progression. Combination with doxorubicin attack on multiple intracellular responses. Combining of cancer drugs with disparate mechanisms of action is a feasible strategy to increase therapeutic efficacy while avoiding unacceptable side effects of the drugs.

Acknowledgements

Authors are thankful to Prof. Pandit Vidyasagar, Hon'ble Vice Chancellor, SRTM University, for his kind support. The authors are also thankful to UGC and DST New Delhi for support under the UGC-SAP DRS II and DST-FIST program respectively.

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