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The Citrus Bioflavonoid Naringin Mitigates Doxorubicin Induced Tissue Toxicity: A Review

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ABSTRACT

Doxorubicin is one of the most important wide spectrum chemotherapeutic agents which are in frequent clinical use to manage numerous neoplasias either alone or in conjunction with other chemotherapeutic drugs. However, induction of cardiotoxicity, hepatotoxicity, pulmonary toxicity and nephrotoxicity along with bone marrow toxicity is the major limiting factor for its optimum use in cancer treatment. This indicates the need to reduce its toxic implication that could help the optimum utilization of doxorubicin in the treatment of cancer. The present review describes the effect of Naringin, a grapefruit bioflavonoid on the management of Doxorubicin induced toxicities in several preclinical studies. Naringin has been found to reduce cardiotoxicity, hepatotoxicity, nephrotoxicity, lung toxicity and DNA damage. The preclinical reports indicate that Naringin deserves clinical application in conjunction with Doxorubicin for the benefit of cancer patients as it is part of daily diet in the form of citrus fruits and juices.

Keywords: Doxorubicin, Naringin, DNA damage, Cardiotoxicity, Reactive oxygen species

INTRODUCTION

Doxorubicin (DOX) 7~{S},9~{S})-7-[(2~{R},4~{S},5~{S},6~{S})-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7~{H} -tetracene-5,12-dione or Adriamycin is an anthracycline group of antibiotic, which was isolated from *Streptomyces peucetius* [1]. DOX is a broad spectrum antineoplastic agent and it has been clinically used either alone or in conjunction with other chemotherapeutic drugs to treat several antineoplastic disorders including Hodgkin's and non-Hodgkin's lymphomas, liver cancers, childhood solid tumors, breast cancer, multiple myelomas, thyroid carcinomas, ovarian cancer, gastric carcinoma, osteosarcoma, acute myeloblastic leukemias, myelogenous leukemia; small cell lung cancer, neuroblastoma, Wilms tumor, Kaposi's sarcoma and soft tissue sarcomas **(Figure 1)** [2-14].

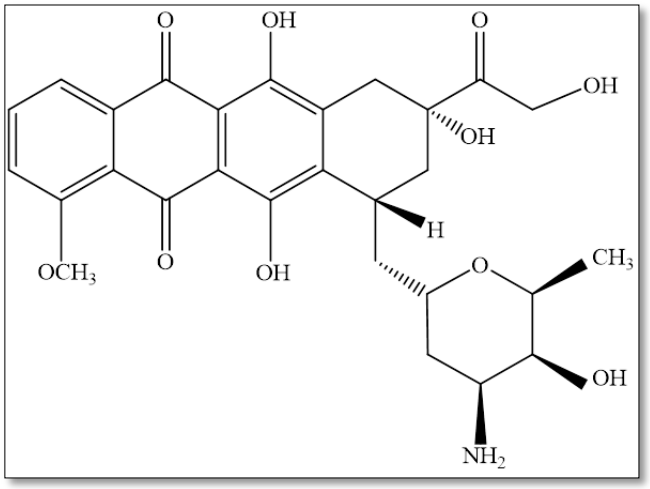

Figure 1. Molecular structure of doxorubicin.

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Despite its high efficacy increasing adverse side effects are major stumbling block in the efficient use of DOX. DOX is known to induce adverse side effects in the form of lacrimation, diarrhea, conjunctivitis, hypersensitivity (fever, chills and urticaria), mucositis, hyperpigmentation of the nails, nausea and vomiting, myelosuppression, alopecia, and discoloration of urine [15,16]. DOX therapy produces tissue toxicity in the bone marrow, brain, kidney and liver [17,18]. Apart from this, the clinical use of DOX is associated with life threatening cardiotoxicity in the surviving patients [19-21]. Despite the fact that it has several side effects, it is clinically successful in treating several neoplasias either alone or in combination with other chemotherapeutic drugs [2-14]. The optimum utilization of DOX in the treatment of cancer can be achieved by concurrent administration of natural products, which may reduce its toxicity without compromising its anticancer activity. The natural products may be more acceptable due to their biologic origin and their use may be also able to counter drug-induced resistance against cancer cell kill.

Naringin (7-(2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy)-2,3-dihydro-4',5,7-trihydroxyflavone) or Naringenin 7-O-neohesperidoside is synthesized as a secondary metabolite by several plants belonging to citrus family **(Figure 2)**. The origin of word Naringin can be traced to Sanskrit word Narangi (orange). Naringin is a disaccharide with a molecular formula of $C_{27}H_{32}O_{14}$ and molecular weight of 580.539 g/mol. Naringin contains two rhamnose units, which are linked to its aglycone portion, Naringenin, at the 7-carbon position. Naringin was first discovered in the flowers of grapefruit tree in Jawa by DeVry in 1857 [22]. Naringin is a bitter tasting, white-beige coloured powder soluble at a concentration of 1 mg/ml in warm water. It is abundant in *Citrus paridisi* (grapefruit), the peels, seeds and membrane of which contain about 0.75% naringin [23]. One liter of grapefruit juice usually contains 800 mg of naringin [24]. Naringin is also synthesized by various other citrus fruits that include *Citrus nobilis* (Tangore), *Citrus junos* (pomelo), *Citrus unshiu* (mandarin orange), *Citrus sinensis* (sweet orange), *Citrus tachibana* (tachibana orange), *Poncirus trifoliata* (bitter orange or hardy orange) and other plants including *Artemisia stolonifera* (wormwood), aerial parts of *Thymusherba barona* (caraway thyme) and roots of *Cudrania cochinchinensis* (cockspur thorn) [25-28]. Naringin forms part of daily diet in the form of various fruits and fruit juices. It has been reported to neutralize various free radicals *in vitro* [29,30]. Naringin also possesses metal chelating activity [31-33]. It possesses a broad-spectrum activity against cardiotoxicity, cancer, carcinogenesis, viral and bacterial infections, liver and nervous system toxicities [34-41]. Naringin has been reported to act as a chemopreventive agent against fore stomach carcinoma triggered by benzo-a-pyrene [42]. It protected against the iron-induced oxidative stress *in vivo* and *in vitro* [32,43,44]. The naringin is active against fibrosis, diabetes, dyslipidemia, inflammation, osteoporosis, lipodystrophy and cognitive damages [45-48]. Naringin has been reported to kill HeLa, AGS and breast cancer cells and also effective against Walker's carcinoma in rats [49-52]. Naringin also protected against LPS-induced lung damage in mice [53]. It has been found to protect against radiation-induced DNA and chromosome damage [30,54]. Naringin has been also reported to reduce radiation-induced oxidative stress in irradiated mice [55]. Naringin has been reported to protect against the bleomycin-induced DNA damage and cell survival in V79 cells [56]. The aim of this review is to focus on the protective effects of naringin against the doxorubicin-induced toxicity.

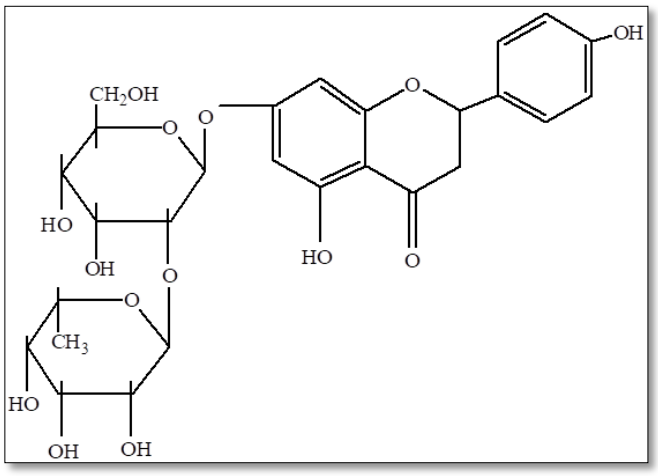

Figure 2. Molecular structure of Naringin (7-(2-O-(6-deoxy-alpha-L-mannopyranosyl)-β-D-glucopyranosyloxy)-2,3-dihydro-4',5,7-trihydroxyflavone).

EFFECT OF NARINGIN ON DOXORUBICIN DISTRIBUTION

The plasma clearance was studied at 0, 1, 2, 3 and 4 h in rats administered with 50 mg/kg Naringin 30 min before 2 mg/kg doxorubicin infusion. The results from this study indicate that oral administration of naringin did not significantly alter the DOX clearance in rat plasma. Similarly, naringin treatment did not alter the excretion of doxorubicin in the rat urine and bile [57]. This study has reported high accumulation of DOX in heart, liver and kidney and naringin administration did not significantly change the distribution of DOX in these tissues [57].

EFFECT OF NARINGIN ON DOX-INDUCED CARDIOTOXICITY

The cardioprotective action of 2.5, 5, 7.5 or 10 mg/kg naringin was investigated in mice treated with 15 mg/kg DOX. The Naringin was orally administered consecutively for five days before DOX treatment and the serum enzymes and antioxidants were studied at 30 h post DOX treatment in the heart homogenate. The results of this study showed that Naringin significantly reduced the cardiotoxicity as

indicated by the decline in the lactate dehydrogenase (LDH), aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) in a dose dependent manner and the maximum reduction was observed for 10 mg/kg body weight of Naringin **(Table 1)**. The study of antioxidants revealed that naringin elevated glutathione (GSH), and activities of catalase and superoxide dismutase (SOD) in a dose dependent manner in the heart of mice treated with DOX **(Table 1)**. This was followed by a significant reduction in the DOX induced lipid peroxidation [40]. A study in Wistar rats has shown that 100 mg/kg Naringin treatment given for 14 days and 15 mg DOX reduced DOX-induced lipid peroxidation and elevated catalase and SOD activities and GSH contents in the heart tissue **(Table 1)**. The histological evaluation of heart has shown that DOX induced inflammation, severe vacuolization, myofibrillar loss, and extensive diffused fibrosis at 96 h after DOX treatment, whereas Naringin administration restored the histology of rat heart to normal [58].

Table 1. Protection of doxorubicin-induced toxicity by Naringin in various tissues in preclinical models.

S. No.	Species	Tissues	Parameters	References
1.	Mice	Heart	Aspartate aminotransferase Alanine aminotransferase Lactate dehydrogenase Glutathione, Catalase, Superoxide dismutase	[40]
2.	Rat	Heart	Glutathione, Catalase, Superoxide dismutase Lipid peroxidation Histology	[58]
3.	Rat	Embryonic heart cells H9c2	Cytotoxicity, Reactive Oxygen Species, p38MAPK	[59]
4.	Rat	Liver	Lipid peroxidation, Glutathione Glutathione-s-transferase, Catalase Superoxide dismutase	[60]
5.	Mice	Liver	Lipid peroxidation, Glutathione Glutathione-s-transferase, Catalase Superoxide dismutase	[61]
6.	Rat	Lung	Glutathione Glutathione-s-transferase, Catalase Superoxide dismutase	[62]
7.	Mice	Bone marrow	Lipid peroxidation, Glutathione Glutathione-s-transferase, Catalase Superoxide dismutase	[63]
8.	Rat	Bone marrow	Lipid peroxidation, Glutathione Glutathione-s-transferase, Catalase Superoxide dismutase	[64]
9.	Mice	Ehrlich ascites carcinoma	Protected against DOX toxicity without compromising its antineoplastic action	[40]
10.	Athymic mice	HeLa cells	Tumor regression Reduced toxicity on Heart, liver and kidney	[65]
11.	Mice	Bone marrow	Micronuclei	[66]
12.	Mice	Heart Liver	DNA adducts	[40]

Embryonic rat heart cells H9c2 treated with 5 µmol/l DOX for 24 h induced cytotoxicity in these cells, whereas pretreatment of H9c2 cells with 0.1, 1, 10 and 20 µmol/l Naringin for two h before DOX treatment significantly reduced the DOX-induced cytotoxicity in a Naringin concentration dependent manner. The optimum effect was observed at 1 µmol/l Naringin. 1 µmol/l Naringin also reduced the formation of reactive oxygen species (ROS) triggered by DOX treatment **(Table 1)**. Naringin treatment

of H9c2 cells also reduced DOX-induced apoptosis in these cells by suppressing p38MAPK [59].

EFFECT OF NARINGIN ON DOX-INDUCED LIVER TOXICITY

Albino rats injected with 5 mg/kg DOX led to a significant increase in lipid peroxidation and reduction in the GSH contents and activities of GST, catalase and SOD, whereas pretreatment of rats with 2 mg/kg body weight of naringin before DOX administration significantly increased the amount of GSH and activities of GST, catalase and SOD and decreased lipid peroxidation in their livers **(Table 1)** [60]. In another study mice injected with 1, 5 or 10 mg/kg of DOX and treated with Naringin at a dose of 10 mg/kg one h before or after DOX treatment showed that DOX treatment enhanced the lipid peroxidation in a dose dependent manner and reduced the GSH contents and activities of catalase, GST and SOD in a similar fashion. Treatment of mice with Naringin 1 h before or after DOX administration significantly reduced lipid peroxidation and augmented the activities of catalase, GST and SOD and GSH contents **(Table 1)**. The effect of pretreatment of Naringin was greater than the post treatment [61].

EFFECT OF NARINGIN ON DOX-INDUCED LUNG TOXICITY

The effect of 2 mg/kg Naringin was studied in albino rats administered with 5 mg/kg DOX. The DOX administration induced biochemical toxicity in the rat lung indicated by a time dependent decline in the GSH concentration and decrease in the GST, catalase and SOD activities, where a maximum reduction in all biochemical endpoints was detected at 2 h post-DOX treatment. Treatment of rats with 2 mg/kg Naringin significantly increased the activities of GST, catalase and SOD followed by a rise in the glutathione contents **(Table 1)**. A greatest elevation was observed at 2 h post-DOX treatment [62].

EFFECT OF NARINGIN ON DOX-INDUCED BONE MARROW TOXICITY

Bone marrow suppression is a dose limiting factor in the optimal use of DOX as a chemotherapeutic agent. The ability of Naringin to reduce DOX-induced bone marrow toxicity has been studied in mice given different doses of DOX before and after Naringin treatment at different times. The mice injected with 1, 5 or 10 mg/kg DOX led to a significant rise in the lipid peroxidation followed by a significant decline in the GSH and activities of GST, catalase and SOD. Naringin treatment at a dose of 10 mg/kg one h before or after DOX administration resulted in a significant decline in the lipid peroxidation at different post-treatment times accompanied by a significant rise in the GSH contents and activities of GST, catalase and SOD **(Table 1)** [63]. The albino rats administered with 5 mg/kg DOX showed an increase in the lipid peroxidation and attrition in the GSH concentration and activities of GST, catalase and SOD from ½ to 2 h post DOX-treatment in the bone marrow. The rats treated with 2 mg/kg Naringin daily for consecutive three days before administration of 5 mg/kg DOX reduced the Lipid peroxidation at ½, 1 and 2 h post-DOX treatment. This was accompanied by a significant rise in the GSH contents, and activities of GST, catalase and SOD **(Table 1)** [64].

EFFECT OF NARINGIN ON THE ANTICANCER ACTIVITY OF DOX

DOX treatment was found to regress Ehrlich ascites tumor in Swiss albino mice accompanied by the induction of toxicity in the heart and liver. Administration of 10 mg/kg Naringin before DOX-administration reduced the cardiac and hepatotoxicity without significantly altering the anticancer activity of DOX in the tumor bearing mice **(Table 1)** [40]. Similarly, a study in nude mice bearing HeLa cells has revealed that treatment of mice with 5 mg/kg DOX reduced tumor volume however; it was accompanied by toxic effect on heart, liver and kidney. The treatment of tumor bearing mice with 20 mg/kg of naringin concomitantly increased the anticancer activity of DOX and at the same time reduced the DOX-induced cardiotoxicity, hepatotoxicity and nephrotoxicity. The treatment of nude mice with both DOX and Naringin was also able to arrest body weight loss triggered by DOX alone, whereas in vitro study in HeLa cells showed that combined treatment of DOX and naringin more efficiently arrested cell proliferation than either treatment alone **(Table 1)** [65].

EFFECT OF NARINGIN OF DOX-INDUCED DNA DAMAGE

DOX is well-known to induce damage to cellular DNA. Treatment of mice with 5, 10 and 15 mg/kg DOX caused a dose dependent rise in the micronuclei in the polychromatic and normochromatic erythrocytes of bone marrow cells followed by the reduction in the cell proliferation as indicated by a decline in the polychromatic and normochromatic erythrocyte ratio. The highest number of micronuclei was observed at 48 h in the polychromatic and 72 h post-DOX treatment in normochromatic erythrocytes. Treatment of mice with different doses of Naringin before DOX administration significantly attenuated the frequency of micronuclei in both the polychromatic and normochromatic erythrocytes at all post DOX treatment times accompanied by a significant rise in the polychromatic and normochromatic erythrocyte ratio **(Table 1)** [66]. The DOX has also been reported to induced DNA adducts at molecular level in the liver and heart of mice, whereas Naringin treatment attenuated the DOX-induced DNA adduct formation significantly **(Table 1)** [40].

MECHANISM OF ACTION

Various mechanisms are involved in the DOX induced cytotoxic effects. However, one of the most important mechanisms by which DOX induces cell killing and it is also

responsible for its toxic effects in various organs is the induction of free radicals or reactive oxygen species (ROS) by DOX. The metabolic activation of DOX into free radical results in its reaction with molecular oxygen leading to the formation of superoxide radicals through redox cycling *in vivo* [67,68]. DOX interacts with NADPH and increase the production of superoxide radicals by activation of Nox-2-NADPH-oxidase and NADPH cytochrome P450 and downregulation of NAD(P)H:quinone oxidoreductase-1 [69,70]. The DOX is known to accumulate iron in the mitochondria [21] and the superoxide radicals thus produced react with hydrogen peroxide in the presence of iron to produce highly reactive and dangerous hydroxyl radicals by Haber-Weiss reaction. These hydroxyl radicals damage DNA and proteins and induce lipid peroxidation inflicting toxic effects to the cells [71]. The doxorubicin interacts with nucleic acids by inter strand cross-linking, equilibrium binding, permanent single covalent attachment, reversible covalent binding, DNA groove and base specific binding, metal ion sequestration and subsequent DNA binding and intercalation with concomitant supercoil relaxation and duplex extension. The redox cycling of DOX causes DNA single strand breaks by phosphotriester formation [72]. The DOX-induced oxidative stress is due to the repression of Nrf2 signaling pathway [73] leading to increased lipid peroxidation and reduction in GSH, catalase, SOD and GST. The DOX is known to mediate its toxicity on cancer cells by inhibiting topoisomerase-II enzyme, which causes DNA single as well as double strand breaks [74]. The DOX triggers the formation of 8-Oxo-2'-deoxyguanosine DNA in adducts the heart and liver of mice [40]. The DOX induces DNA adducts independent of topoisomerase II suppression. The induction of doxorubicin-DNA adducts triggers activation of caspases that leads to apoptosis [75]. DOX has been found to overexpress p38 mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB), COX-2, iNOS, TNF-α, TLR4 signaling and nitric oxide causing cell killing [8,76-78]. It also activates DNA damage response by upregulating phosphorylation of ATM, P53, CHK1, CHK2 and γH2AX genes [79]. The DOX-induced hydroxyl radicals play a major role in the activation of ATM pathway and cell cytotoxicity [80]. The activation of ATM dependent Chk2-DNA damage response pathway by DOX causes arrests of cells in G2+M phase of the cell cycle leading to cytotoxicity [81]. The DOX has been reported to activate poly (ADP-ribose) polymerase (PARP) *in vitro* and *in vivo* and upregulate p53 to trigger cytotoxicity [66,82,83]. DOX also impairs electron transport in the mitochondria [84].

The reduction in DOX-induced toxic effects by Naringin may be due to its ability to target several pathways triggered by DOX to induce cytotoxicity. The Naringin has been reported to scavenge various free radicals [29,30,85] and presence of Naringin would have suppressed the DOX-induced free radicals that may have reduced toxic effects of DOX. The iron chelating property of Naringin [31-33] would have restricted the availability of iron leading to inhibition of the formation of DOX-induced hydroxyl radical. This would have down modulated the ATM dependent pathway reducing the cytotoxic effect as well as DNA damage triggered by DOX. Naringin suppresses the ROS mediated MAPK (p38 MAPK, ERK1/2 and JNK) signaling pathway [86]. It also inhibits NF-κB signaling and COX-2 pathways and upregulates Nrf2 pathway [87-89] leading to abrogation in the DOX-induced decline in various antioxidants including GSH, GST, catalase, SOD, and glutathione peroxidase (GSHpx). The attenuation of DOX-induced cytochrome P450 activity by Naringin may have also contributed to reduced toxicity of the former as the Naringin has been found to inhibit cytochrome P450 activity [90,91]. The suppression of PARP activity by Naringin [40] is also responsible for attrition of DOX-induced cytotoxicity. Naringin is metabolized into its aglycone form Naringenin by human intestinal bacteria [92,93], which attenuates the expression of NF-κB, MAPK, TNF-α, IL-6, TLR4, inducible NO synthase (iNOS), NADPH oxidase-2 (NOX2) and COX-2 which are all overexpressed by DOX. The restoration of topoisomerase-II activity by Naringin may have also played an important role in reducing the DOX-induced cytotoxicity.

CONCLUSION

DOX is an important antineoplastic drug used for the treatment of several malignancies either alone or in combination with other chemotherapy agents. The main impediment in the optimum utilization of DOX in cancer therapy is induction of cardiotoxicity, myelosuppression, pulmonary, hepato- and nephro-toxicities in patients receiving this drug either alone or in conjunction with other chemotherapeutic agents. Naringin treatment has reduced toxicities in heart, lung, liver, kidney and bone marrow in preclinical systems. The main mechanism of DOX-induced toxicity is due to its ability to trigger the formation of ROS that stimulate a host of genes including NF-κB, COX-2, MAPK, iNOS, TNF-α, TLR4, ATM, p53, CHK1, CHK2, γH2AX and PARP that induce DNA damage and activation of caspase cascade causing cells death due to apoptosis or necrosis. The use of naringin has been found to reduce biochemical toxicities in heart, kidney, liver, lung and bone marrow. This reduction in the DOX-induced toxicity by Naringin is mediated by attenuation of DOX-induced free radicals and suppression of various proteins-induced by DOX listed above. The Naringin may have also suppressed DOX intercalation into the DNA and abrogated the topoisomerase-2 inhibition. The results from preclinical studies indicate that Naringin deserves attention as a drug that can be used in combination with DOX to reduce the toxic effect of latter.

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CONFLICT OF INTEREST STATEMENT

Author does not have any conflict of interest statement to declare.

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