DEEPER INSIGHTS INTO IMPACT OF ANTIOXIDANTS ON ANTICANCER DRUG-INDUCED LIPID PEROXIDATION: AYE AND NEY

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Abstract:

Anticancer agents are associated with a plethora of side effects. Individual agent, within each category, has its own set of adverse reactions based on specific mechanism which in turn cause patient incompliance and deterioration of the quality of life. Among the different adverse reactions, the major one is drugs targeting the DNA, where there is an excessive production of reactive oxygen species (ROS) and subsequent buildup of oxidative stress. Several dietary supplements have been proposed by different researchers to curb these undesired side effects, amongst which antioxidants have gained increasing popularity as an adjuvant in chemotherapy.Cancer patients received chemotherapy may develop various kidney lesions that impair their life style, immediate survival as well as limit the adequate treatment of the underlying malignant process.The side effects associated with anticancer drugs are vomiting, stomatitis, diarrhea,desquamation of skin, alopecia, bone marrow depression, hepatotoxicity, ototoxicity, nephrotoxicity, cardiotoxicity and many more. There are many mechanisms developed to describe the consequences of drug toxicity. One of them is lipid peroxidation. Peroxidation of lipid results in progressive deterioration of membrane structure and loss of proper functioning of cell in the presence of oxygen free radicals. All drugs are required to cross the omnipresent membrane to produce desired pharmacological action. The drugs may cause perceptible or detectable changes in the lipid profile while crossing the membrane phospholipids. So, drugs are the potential candidates to initiate lipid peroxidation. As lipid peroxidation is one of the reasons of drug toxicity, this article is a review of anticancer drugs that have the capacity to induce lipid peroxidation as a basis of adverse effects and significances of antioxidant as a suppressor of anticancer drug-induced lipid peroxidation.

Keywords: Llipid peroxidation, antioxidants, anticancer drugs, adverse effects, drug toxicity

Introduction

Biological membranes are very prone to oxidative damage. Peroxidation of lipid results in progressive deterioration of membrane structure and loss of proper functioning of the cell. In general, oxidative degradation of cholesterol and phospholipids containing polyunsaturated fatty acids (PUFA) are called lipid peroxidation [1]. The damage of both PUFA and cholesterol are facilitated by enzymatic and non-enzymatic lipid peroxidation pathways shown in **figure 1**. Non-enzymatic oxidation of lipids can be of free radical-mediated or free radical independent [2]. Peroxidation of PUFA results from the interactions of free-radicals with cholesterols and phospholipids takes place through five basic elementary reactions. These are (i) hydrogen atom transfer from PUFA to the chain carrying peroxyl radicals, (ii) reaction of the lipid radical with molecular oxygen, (iii) fragmentation, (iv) rearrangement and (v) Cyclization of the proxy radical [3-4]. Lipoxygenases (LOX), cyclooxygenases (COX) and cytochrome P-450 (CYP) participate in the enzymatic degradation of arachidonic acid (AA), a phospholipid to form hydroperoxyeicosatetraenoic acids (HPETEs), lipoxins, leukotrienes, epoxyeicosatrienoic acids, leukotoxins, and thromboxane as oxidative products of lipid. Non-enzymatic oxidation is known as auto-oxidation of lipids. Auto-oxidation is a spontaneous free radical chain reaction in which oxygen and transition metal produce superoxide or hydroxide free radicals by hemolysis of endogenous hydroperoxides [5-7].

Cells, tissues, and organs injuries are the magnitudes of oxidative damage results from lipid peroxidation. High levels of reactive oxygen species (ROS) can cause direct damage to lipids, proteins, or DNA [8-9]. Lipid peroxidation leads to many pathological conditions and toxic manifestations. They include liver injury, atherosclerosis, intermittent claudication, neuronal ceroidlipofuscinosis, structural derangement of the lipid bi-layer, increased the permeability of cytosolic constituents, inactivation of intrinsic enzymes and much more [1, 10-11].

To prevent the consequences of lipid peroxidation, cells produce manganese superoxide dismutase (Mn-SOD) and zinc or copper superoxide dismutase (Zn/Cu-SOD) from liver and stored them into mitochondria and cytosol respectively. They convert superoxide to hydrogen peroxide when required by the cells. Hydrogen peroxide is then catalyzed by catalase enzyme into water and oxygen. Glutathione and nitric oxide also help to prevent the damage from ROS. Reduced glutathione and nitric oxide are the two most important antioxidants produced by the body to protect cells from oxidative damage. Reduced glutathione (GSH) is a linear tripeptide of L-glutamine, L-cysteine, and glycine found in liver contain a sulfhydryl (SH) group on the cysteinyl portion, which accounts for its strong electron-donating character. It acts by quenching reactive hydroxyl free radicals, other oxygen-centered free radicals, and radical centers on DNA. It is a primary protectant of skin; lens, cornea, and retina against radiation damage [12-16].

Nitric oxide is secreted from the vascular endothelial cell in blood. Lipid oxidation can also be initiated by ferryl hemoglobin, formed from the interaction of hemoglobin with peroxides. Nitric oxide has been shown to reduce the ferrylheme and so prevent lipid oxidation by this mechanism [17]. According to the free radical hypothesis in term of oxidative stress, the damage is caused by a shift in the balance between the pro-oxidative and anti-oxidative processes

in the direction of the pro-oxidative state. This increases the chances of cancer, angiogenesis, carcinogen metabolism, and metastasis [10, 18].

Anticancer drugs are used to kill the uncontrolled proliferating tumor cells of our body. Due to narrow therapeutic index, high dose of these drugs is often used to achieve the desired therapeutic response. The normal tissues such as rapidly proliferating normal cells of bone marrow, gastrointestinal tract and hair follicles are also affected along with abnormal cells during the chemotherapy. Adverse effects are one of the leading causes of failure of most antineoplastic agents. Some common adverse effects associated with anticancer drugs are drowsiness, lethargy, tiredness, fatigue, insomnia, dizziness, unsteadiness, vertigo, imbalance, ataxia, diplopia, tremor, cognitive impairment, irritability, aggressive behavior, depression; gastrointestinal symptoms etc [19-21]. There are many mechanisms developed to describe the adverse effects produced by anticancer drugs. Lipid peroxidation is one of them. As most of the drugs have to pass through the omnipresent membrane and phospholipid is one of the components of the cell membrane, are very liable to induce lipid peroxidation [22].

Antioxidants are the substances that protect cells from the injury caused by free radicals. They are capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by eliminating free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. The free radical injury may lead to cancer also. Antioxidants may play a very important role in the management of cancer chemotherapy [23]. Examples of antioxidants include beta-carotene, lycopene, phenolic acid, flavonoids, vitamins C, E, A, and other naturally occurring substances [24-30].

The central theme of this review article can be stated in few words. The development of a new drug requires a huge investment of money and time. Whereas their many drugs available in the market whose applications are limited as they show moderate to severe toxicity. If the toxicity is optimized then the therapeutic efficacy of those drugs could be improved. We know that therapeutic index of a drug depends on Toxic Dose (TD_{50}) / Effective Dose (ED_{50}) values. If toxic dose increased then the therapeutic index can be improved which is shown in **figure 2**.

It means that the drug will show toxic effects in a higher dose. But how the toxicity can be improved? As lipid peroxidation is one of the causes of adverse effects shown by the anticancer drugs [23, 31-32], the use of antioxidants co-therapy during the cancer chemotherapy could be a useful tool to optimize or reduce the chances of adverse effects produced by them.

Mechanism and toxicological manifestations of anticancer drugs as a consequence of lipid peroxidation

The basic mechanism through which most of the anticancer drugs acts is summarized in **figure 3.** As antineoplastic agents act by participating in cell division, they must cross the cell membrane to interact with DNA and their bases. It is believed that most of the anticancer drugs kill cells, primarily through a programmed, energy-dependent process

called apoptosis, rather than through cell necrosis. Different classes of anticancer drugs show the different mechanism of cell apoptosis. Antimetabolites inhibit DNA synthesis whereas alkylating agents and antibiotics damage or disrupt DNA by interfering topoisomerase activity or alter ribonucleic acid (RNA) structure. Steroids interfere with transcription, several plant alkaloids interrupt mitosis, asparaginase destroys essential amino acids needed for translation, and other drugs act through important growth factor signal transduction pathways. Many clinically used antineoplastic agents undergo either chemical or enzymatic modification to exhibit cytotoxicity [20, 33]. While producing desired therapeutic effects they induce nephrotoxicity, ototoxicity, neurotoxicity, hepatotoxicity, cardiotoxicity as major adversativeeffects.

Nephrotoxicity

Acute renal toxicity is one of the most observed side effects exposed by anticancer drugs like cisplatin and ifosfamide [34-38]. Ifosfamide showed nephrotoxicity in children endured cancer chemotherapy. It reduces glutathione concentration and inhibits glutathione-S-transferase activity by inducing lipid peroxidation, leads to typical morphological damages in renal tubules and glomeruli [39-40]. The clinical application of cisplatin is limited due to its capability to produce nephrotoxicity.Nephrotoxicity showed by cisplatin is a magnitude of lipid peroxidation in kidney cortex [41-43].

Ototoxicity

Carboplatin is a second generation platinum-containing anticancer drug. It is used in the treatments of small-cell lung cancer, ovarian cancer, and carcinoma of the head. Carboplatin persuaded high-frequency hearing loss which is related to a depleted concentration of GSH, inhibition of antioxidant enzyme activities, depletion of enzyme Mn-SOD activities and enhanced lipid peroxidation in the cochleae [44-45]. Oxaliplatin, another drug of this category, widely used in the treatment of colorectal cancer show severe side effects such as neuropathy, ototoxicity, gastrointestinal toxicity, and hematological toxicity. Studied showed that the toxicity associated with oxaliplatin was the results of induced lipid peroxidation in cochleae and microsomal cells [46].

Hepatotoxicity

Topotecan, a semi-synthetic derivative of camptothecin, exhibited hepatotoxicity as a side effect by increasing the concentration of peroxide radicals and decreased in antioxidant enzyme activities in liver cells [47]. Flutamide, an androgen produced hepatotoxicity by decreasing GSH content in isolated rat hepatocytes [48]. Phototoxicity of flutamide both in aerobic or anaerobic conditions was mediated by photosensitization and concomitant singlet oxygen production [49-50]. Flutamide prompt hepatotoxicity by increasing cellular oxidative stress [51].

Cardiotoxicity

Adriamycin, epirubicin, and daunorubicin promoted the lipid peroxidation in liver and heart microsomes by reducing the activity of cytochrome P-450 reductase. The major side effect related to this drug is cardiotoxicity [52-53]. The

anthracyclines, such as doxorubicin and epirubicin, are potent cytotoxic drugs but clinical use of these drugs was often limited due to cardiotoxic side effects. Other cytotoxic drugs that were reported cardiotoxicity include 5-fluorouracil, capecitabine, mitoxantrone, cisplatin, the toxoids paclitaxel, and docetaxel. Lipid peroxidation was found to be the causative factor of this toxicity. The possible susceptibility of the cardiac cells to the oxidative stress would be due to relatively low levels of antioxidant enzymes in the heart [54-58]. Doxorubicin showed cytotoxic effect through the generation of superoxide radicals in the human breast tumor cell line MDA-MB-231. Experiment on microsomal cells confirmed cardiotoxic effect due to the increased concentration of lipid hydroperoxide in cardiac muscles [59-60].

Miscellaneous

The clinical uses of bleomycin as an antineoplastic drug are restricted due to its ability to produce pulmonary fibrosis [61]. The ability of bleomycin to induce lipid peroxidation in the liver and lung microsomes reported recently. It abridged microsomal GSH concentration [62-64].Letrozole caused polycystic ovary (PCO) in the rat. A significant increased in cellular lipid peroxidation (LPO) and peroxynitrite (ONOO.) radical after the administration of letrozole revealed its capacity to induce lipid peroxidation. Also, it decreased the ovarian concentration of SOD, catalase (CAT) and glutathione peroxidase (GPx) during the therapy [65].Mechlorethamine, chlorambucil, cyclophosphamide, carmustine, and lomustine are nitrogen mustered readily induced cytotoxicity in isolated rat hepatocytes. Depletion in the concentration of GSH, Nitric oxide (NO) and generation of 4-HNE in blood confirmed lipid peroxidation induction capacity of the drugs [66-71]. The in-vivo experimental study was carried out to establish the mechanism of the adverse effect produced by paclitaxel in Wister rat. The study revealed that paclitaxel-induced lipid peroxidation as a consequence of toxic side effect [72].Romidepsin is used to treat leukemia. It stimulated hydrogen peroxide activity to lift apoptosis of normal cells as a toxic side effect [73].

Effects of antioxidant on cancer and anticancer drug-induced lipid peroxidation

Apoptosis and cancer are opposite phenomena, but ROS have been widely reported to play a key role in both. There isevidence that apoptosis can be induced by ROS and induction of intracellular production of ROS is inhibited by the addition of antioxidants [74]. Although the mechanism involved is still controversial, but the redox status and hydrogen peroxide both have been proposed as critical factors. In addition, induction of carcinogenesis has been clearly linked to oxidative DNA damage. The oxidative product of DNA, 8-oxo-2'-deoxyguanosine, was reported to be highly mutagenic in nature. ROS are thought to contribute to carcinogenesis through interference with signal cascade systems, including the nuclear transcription factor kappaB (NF-kB), activated protein-1 (AP-1), phospholipase A2, mitogen-activated protein kinases (MAPKs) and c-Jun kinase. Cells react rapidly to redox imbalance [75-77].

Vinorelbine, vincristine, vinblastine, and vindesine are vinca alkaloids used to control the growth of proliferative malignant cancer cells. These class of drugs produced ROS which leads to DNA damage and mitochondrial dysfunction of normal cells along with adrenocarcinoma cells [78]. Lenalidomide, an analog of thalidomide is a potent inhibitor of

tumor necrosis factor alpha (TNF-α). It initiates lipid peroxidation to induce cellular apoptosis [79]. NF-κB is a potential therapeutic target for acute myelogenous leukemia (AML). Niclosamide showed antineoplastic activity by inhibiting the NF-κB pathway in AML cells. It increased ROS levels to induce apoptosis [80].

From the above-mentionedevidence, it is well understood that the use of antioxidants not always beneficial during cancer chemotherapy as many anticancer drugs induce cell apoptosis by generating ROS. In the same time, it has been evidenced that anticancer drugs induced toxicity as a consequence of the formation of ROS. So, in those cases, anantioxidant can play a very key role to reduce/suppress the undesired effects induced by the drugs. The followings are some antioxidants displayed significant effects in lower the lipid peroxidation induced by anticancer drug as a consequences of adverse effects.

Ascorbic acid

Ascorbic acid or Vitamin C, a potent antioxidant, abundantly seen in nature showed a potential role to reduce cisplatin-induced lipid peroxidation in liver tissue homogenates [79]. Flutamide- and paclitaxel-induced lipid peroxidation can also be prevented by using ascorbic acid. It improved the therapeutic index of the drug by reducing toxicity, which may be mediated by free radical mechanisms [71, 81-83].

Caffeic acid

Effect of caffeic acid onto the interaction of DNA-anticancer drug was evaluated. Daunorubicin (DNR) was used for this study. The interaction efficiency between DNR and DNA was examined both in the presence and absence of caffeic acid. The study revealed that use of caffeic acid has both beneficial and complicated effects on DNR chemotherapy. [84]

Curcumin

Effects of curcumin on cisplatin- and oxaliplatin-induced oxidative stress in human embryonic kidney (HEK) 293 cells was carried out to explore the protective effects of antioxidants on anticancer drug-induced toxicity. The study revealed that curcumin improved the therapeutic index of both the drugs by reducing the oxidative stress during the treatment [85].

Epigallocatechingallate (EGCG) andtheaflavin (TF)

Tea (*Camellia sinensis*) and its polyphenols like epigallocatechingallate (EGCG) and theaflavin (TF) exhibited potential anticancer activity in pre-clinical and clinical studies. The study found that the mechanisms through which tea and its polyphenols work were as anti-oxidant which induced detoxification system thereby inhibiting carcinogen metabolism and cancer initiation [86]

GSH and phenolic antioxidants

Cisplatin-induced nephrotoxicity was prevented by thiols (GSH and DTT) and phenolic antioxidants (DPPD and BHA) in renal cortical slices. The depletion of cellular thiols and the initiation of lipid peroxidation contributed to the cisplatin-induced nephrotoxicity [87].Docetaxel is a semi-synthetic derivative of paclitaxel produces several toxic side effects due

to damage of normal cell-like hair follicles, bone marrow, and other germ cells. Docetaxel has the capability of inducing lipid oxidization and membrane damage in human hepatoma cells. The effect of antioxidant on docetaxel-induced lipid peroxidation was explored and found that using antioxidant can reduce the chances of the adverse effect produced by docetaxel [88].

Hesperetin

Cisplatin-induced ototoxicity was prevented by hesperetin, a flavonol obtained from plant origin. It increased antioxidant enzymes activity and reduced oxidant parameters in proliferating cochlear cells [89].

Myricetin and gossypol

Myricetin and gossypol are two plants derived antioxidants of quercetin family shown protective effects on bleomycin-induced DNA damage through the inhibition of peroxide free radicals [90]. The ability of bleomycin to enhance ion-catalyzed damage observed during the treatment can be protected by using any phenolic compounds concurrently [91]. An experimental study was carried out to determine the protective effects of quercetin on epirubicin-induced acute oxidative stress toxicity in rat liver cells and mitochondria. The results suggested quercetin, as a potent antioxidant to reduce the risk of epirubicin-induced acute toxicity [92].

Melatonin

Melatonin is a potent antioxidant. It worked by a) scavenging free radicals b) stimulating antioxidative enzymes, c) increasing the efficiency of mitochondrial oxidative phosphorylation and thereby lowered free radical generation [93-94]. It showed protective effects against Mitomycin C-Induced genotoxic damage in peripheral blood of rats [95-96]. Tamoxifen is extensively used in the treatment of breast cancer. It exposed increased microsomal membrane fluidity as an adverse effect. Melatonin reduced the risk of microsomal damage encountered by free radicals [97]. Melatonin was found to be effective in epirubicin-induced cardiotoxicity [98].

Morin

Morin, a member of flavonols, exert antioxidant potential and offer protection against the oxidative stress induced by hydrogen peroxide. Morin inhibited cyclophosphamide-, flutamide- and busulfan-induced lipid peroxidation both in goat liver and white New Zealand rabbit [99-103].

Polyphenols

Polyphenols possess excellent anti-oxidant, anti-inflammatory properties [104]. It also modulates cell signaling pathways leading to anti-cancer effects. Promising results of in-vitro and in-vivo experiments were observed while combinations of polyphenols and chemotherapeutic agents used. This opened up new avenues for the discovery of the ideal drug combinations for cancer chemotherapy [105]. It was also found that polyphenols played a very effective role

in the reduction of oxidative stress in cancer [106]. Polyphenols obtained from green tea found to possess effective against antibiotic anticancer drug-induced lipid peroxidation as a consequence of toxic side effects [107].

Silymarin

Silymarin, an extract of Silybummarianum seeds contain silybin, silydianin and silychristin as active constituents showed antiperoxidative potential on doxorubicin-induced oxidative stress in rat liver microsomes and mitochondria. It protected rat heart microsomes and mitochondria against iron-dependent doxorubicin-induced lipid peroxidation [108].

Virgin olive oil and selenium

Adriamycin-induced cardiotoxicity can be prevented by using nutrients containing antioxidants such as vitamin E, vitamin C, vitamin A, coenzyme Q, flavonoids, antioxidant components of virgin olive oil and selenium [109].

Antioxidants as pro-oxidants

Pro-oxidants are chemical entities that induce oxidative stress either by producing ROS or by inhibiting antioxidant systems of cells [110]. Several anticancer agents derived from natural plant products used in the treatment of hematological malignancies cause an imbalance of the cellular redox status. These pro-oxidants induce their cytotoxicity by impacting on signaling pathways that are generally facilitated by apoptosis or autophagy [111]. Antioxidants scavenge ROS and maintain the balance between ROS and antioxidant system. But studies showed that polyphenols which act as an antioxidant, such as flavonoids tannic acid, gallic acid, curcumin, gallocatechin cause oxidative breakdown of DNA strand either alone or in the presence of transition metal ions such as copper, iron etc [112-113]. The potential of phenolic antioxidants to undergo decomposition reactions leads to the formation of products exerting pro-oxidant activity. A hydroalcoholic solution containing caffeic acid was assessed for both antioxidant and pro-oxidant activity and found that on heating caffeic acid decomposed to induce pro-oxidant effects on cells [114-115]. Grow-Chin Yen et al. investigated the antioxidant and pro-oxidant properties of ascorbic acid (AbA) and Galic acid (GA). The investigation showed that the both have pro-oxidant effects along with antioxidant property at a lower concentration. The pro-oxidant action of AbA and GA at lower concentrations may be due to their weak metal-chelating effects, their strong electron-donating effects and their potentials to stimulate oxidation [116]. The pro-oxidant activity of AbA can be a useful tool in malignancies [117].

Conclusion

Lipid peroxidation induced by anticancer drugs results in several toxic side effects such as hepatotoxicity, ototoxicity, nephrotoxicity, cardiotoxicity, mitochondrial dysfunctions and apoptosis of thenormal cells. Antioxidants can play a very important role to counter act the toxicological manifestations of chemotherapeutic agents by scavenging the peroxide free radicals produce by these drugs during the therapy. But, many antioxidants show pro-oxidant activity in a dose-dependent manner. Moreover, anticancer drugs that generate ROS for tumor cell apoptosis, an antioxidant may induce

a negative result while administered along those drugs. This review will help the researcher and clinicians to understand the benefits as well as contradictory effects of antioxidants to reduce the toxicity produced by anticancer drugs and proper use of antioxidants in cancer chemotherapy.

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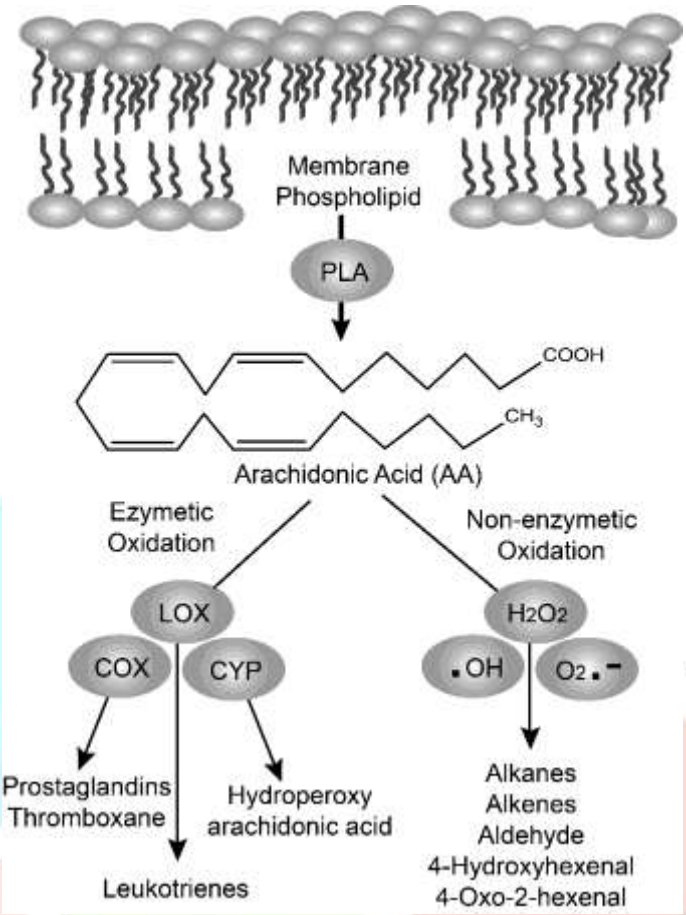
Figure 1: Lipid peroxidation pathways of membrane phospholipid



Foot Note:PLA (Phopholipase-A), COX (Cycloxygenase), LOX (Lipoxygenase), CYP (Cytochrome P_{450}), .OH (Hydroxyl free radical), H_2O_2 (Hydrogen peroxide), $O_2^{\cdot-}$(Superoxide free radical).

Figure 2:*Relationship of Therapeutic index with Toxic dose$_{50}$ and Effective dose$_{50}$. TI increases when TD$_{50}$ value of a drug increases.*

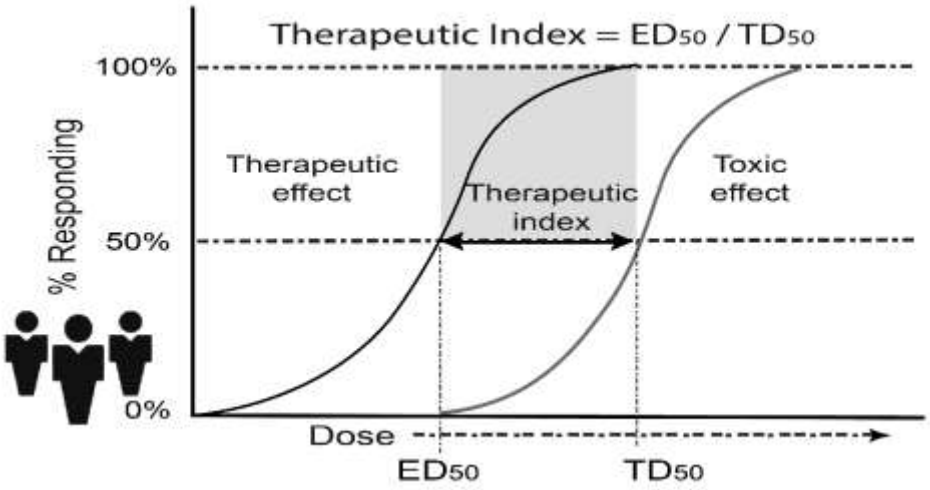


Figure 3: Mechanism of action of anticancer drugs.