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*Review*

# Antitumor antibiotics: representatives, mechanisms of action and side effects

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## Abstract

Bacteria and fungi synthesize various compounds necessary for their own metabolism, as well as compounds that kill other microbial strains and species from the environment in which they grow, to ensure their access to sufficient supplies. Since the discovery of their antitumor effect, three main classes of antibiotics are used in cancer therapy: anthracyclines (secondary metabolites, mainly produced by members of Streptomyces group, or semisynthetic derivatives containing the 7,8,9,10-tetrahidrotetracen-5.12 quinone structure), peptide antibiotics and quinolones. In this minireview, we will present the mechanisms of action, main representatives and side effects of these anti-cancer agents.

**Keywords** antitumor agents, anthracyclines, peptide antibiotics, quinolones

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## Introduction

Bacteria and fungi synthesize various compounds necessary for their own metabolism, as well as compounds that kill other microbial strains and species from the environment in which they grow, to ensure their access to sufficient supplies. In 1909, American bone surgeon and cancer researcher William Coley (1909) has prepared native supernatants from pure culture of *Streptomyces pyogenes* and *Serratia marcescens*, which he administered to 1200 neoplastic patients. The results were encouraging: tumour regression in 52 of them, and out of these, 30 patients were completely recovered. Its discovery preceded with 19 years the discovery of the very first antimicrobial compound, penicillin, by Alexander Fleming, in 1928, which opened a new era in infections treatment. Since then, the antibiotic classes of anthracyclines, peptides and quinolones, were proved to have specific inhibitory effects on tumour cells and anti-bacterial cells, some of their members being used as anti-cancer agents with high clinical importance (Rao et al., 1962). The purpose of this minireview is to present the mechanisms of action, main representatives and side effects of these anti-cancer agents.

## Anthracyclines

*Anthracyclines* are polyketides (condensed planar heterocycles) containing anthracene as core structure (fig.1). Polyketides are complex molecules, belonging to the group of actinobacteria secondary metabolites, mainly synthesized by members of *Streptomyces* group, or to the semisynthetic derivatives containing 7,8,9,10-tetrahidrotetracen-5.12 quinone structure. According to Katz & Donadio (1993), there are two classes of polyketides: aromatic and complex. They have both antitumor and antibacterial activity. The first members of this group of compounds were reported by Brockman and Bauer (1950) and their use as anti-tumour agents started with daunorubicin discovery. Natural anthracyclines are isolated from fungal species, while the synthetic ones are obtained by glycosylation with rodosamine (including *amino* sugars), *daunosamine* and neutral glycosides. Some of them, such as aglycon, are usually inactive, but amongst hundreds of anthracyclines molecular analogues with antitumoral and antimicrobial activity, FDA approved a small number for clinical administration: *actinomycin D* (dactinomycin), *daunorubicin*, *doxorubicin*, *epirubicin*, *idarubicin*, *mitomycin*, *mitoxantrone*, *plicamycin*, *valrubicin*, *enediyne*, *guanorycin*, etc. (Saeidnia, 2015). Some of these are active, especially after chemical change, irrespective of cell cycle stage, even in G0, inhibiting proliferation, acting as pro-apoptosis and anti-epithelial-mesenchymal transition factors, thus inhibiting metastasis (Zhou J, 2013). Anthracyclines inhibit oxidative phosphorylation in mitochondria, inhibit DNA and RNA polymerases, DNA repairing enzymes, metallothionein synthesis (a protein synthesized by intestinal epithelial cells that inhibits Cu absorption, its synthesis being stimulated by Zn), topoisomerase I and II, helicase, stimulates free radicals release and the non-nucleolytic cleavage (Robert J & Gianni L, 1993).

*Doxorubycin* (adriamycin) was isolated from *Str. peucetius* and is a cytotoxic antibiotic with major importance in different types of neoplasia, including pediatric cancer (Hayward et al., 2013, Preet et al., 2015, Gao Yuan et al., 2020; Cheng et al., 2017). It has an amphiphilic (amphipathic) molecule; the water insoluble anthracycline ring is lipophilic and the saturated end of the cycle with numerous –OH groups associated with aminated carbohydrate daunosamine forms a hydrophilic center. The molecule is amphoteric because contains acid functions in phenolic groups and alkaline ones in the amino group of the carbohydrate. Doxorubycin binds to the cell membrane and plasmatic proteins and disturbs numerous cell functions. Enzymatic reduction of doxorubicin, by electron acceptance under the action of oxidases, dehydrogenases and reductases generates extremely active species, including free $OH^{\bullet}$ radicals. Doxorubycin is also a DNA intercalating agent, blocking DNA and RNA replication and transcription and thus protein synthesis in cells with high growth and division rate. It also interacts with topoisomerase II forming complexes that break the DNA molecule. Cardiotoxicity of doxorubycin is explained by the inhibitory activity on topoisomerase and glutathione peroxidase, leading to increased oxidative stress in the absence of catalase in these cells (Thorn et al., 2011; Cagel et al., 2017; Hayward et al., 2013; Takemura & Fujiwara, 2007, Minotti et al., 2004).

*Daunorubicin* (daunomycin) is a glycoside derivative of anthracycline fermentation which contains an anthraquinone ring and daunosamine (an amino sugar). Daunorubicin rapidly penetrates cell, it accumulates in nucleus, intercalates in the DNA strand and daunosamine stabilizes the complex by additional interactions making the difference between daunorubicin and other intercalation agents as ethidium bromide – which establishes interactions only in the intercalation site. Another probable target being topoisomerase II, daunorubicin is an efficient inhibitor of DNA replication and transcription. By oxidation and reduction of anthraquinone, daunorubicin can generate cytotoxic free $O2^{\bullet-}$ radicals, explaining the cumulative cardiotoxicity (Bloomfield et al., 1973; Marco et al.,1977).

*Epirubicin* is a DNA intercalating chemotherapeutic agent and also a topoisomerase II inhibitor (Cragg & Newman, RAPT vol 33) (Waters et al., 1999).

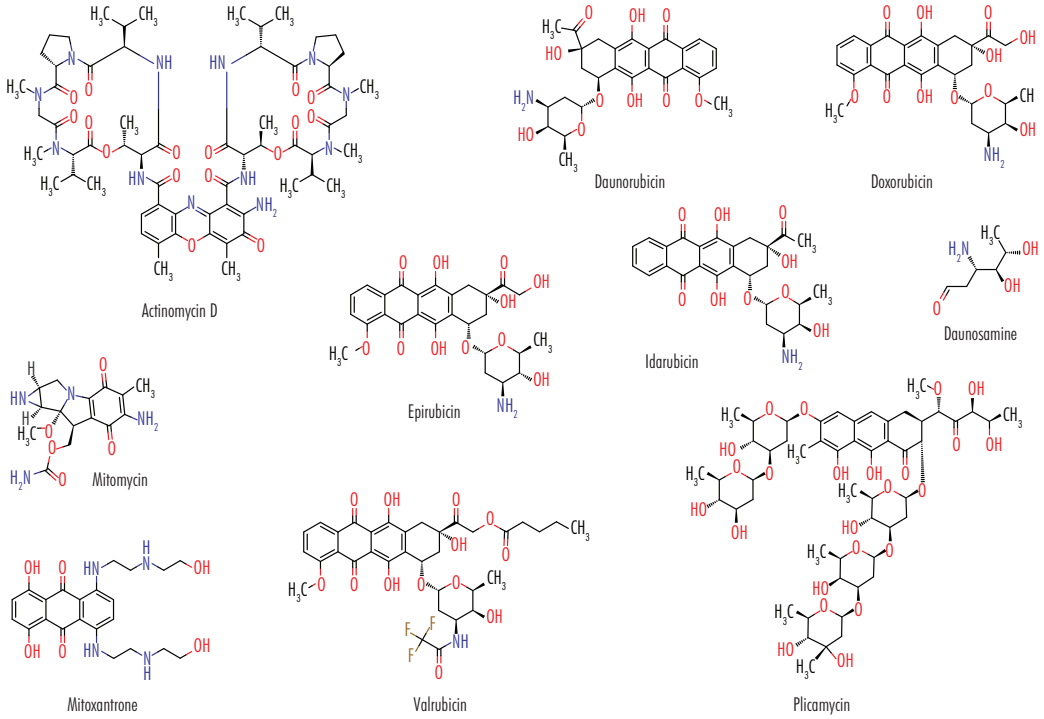


Figure 1. Chemical structures of some members of the anthracycline family, synthesized by microorganisms and having antimicrobial and antitumor activity. Actinomycin D is also a member of the peptide class of antibiotics which act as antimicrobial and antitumor agents.

*Mitoxantrone* (anthracenedione) inhibits lipid peroxidation, has a low toxicity to cardiac muscle, it contains no carbohydrate groups and produces no reactive oxygen species (Fox et al., 1986).

*Plicamycin* has inhibitory effect against several neoplasia. It binds DNA sequences rich in GC in any stage of cell cycle, inhibits RNA and protein synthesis (Thurlimann et al., 1992).

*Idarubicin* is an anthracycline antibiotic with antimitotic and cytotoxic activity acting by DNA intercalation and topoisomerase II inhibition (Robert J & Gianni L, 1993).

The three members of mitomycin family: mitomycin A, mitomycin B, and mitomycin C are isolated from *Str. caespitosus*. After activation inside the cell by a reductase, mitomycin binds on a DNA single chain by alkylation, but also forms transversal links between chains. The effect is DNA depolymerization, with replication, transcription and protein synthesis inhibition (Verweij et al,1990; Tomasz & Palom,1997, Bradner, 2001).

## Peptide antibiotics

*Actinomycines* are a family of 50 chromopeptide antibiotics, but only two have therapeutic value. Actinomycin D (dactinomycin) is synthesized by *Str. antibioticus* on a variety of chemically defined media and on complex organic media, and it is the first antibiotic which was proved to have antitumor activity (1943). Its molecule contains an aromatic group (polyphenolic ring) that binds with two cyclic polypeptide chains (fig. 2). Actinomycin D interacts with absolute specificity with deoxyguanine in DNA, similarly in eukaryotic and prokaryotic cells: the aromatic ring intercalates inside the DNA double helix at GC pairs, and the cyclic peptide remains outside and induces single and double strand breaks. Actinomycin D also inhibits RNA polymerase (inhibiting replication and transcription) and has played an important role in mRNA discovery. After RNA polymerase-catalyzed transcription is blocked, the synthesis of all forms of RNA, including those undergoing synthesis, is stopped. The antibiotic is not active on Gram negative bacteria because of reduced permeability, but spheroplasts are sensitive. Actinomycin D does not bind to RNA or mcDNA, and its affinity for double-stranded DNA depends on the guanine content, as synthetic double-stranded polynucleotides do not interact with the antibiotic (Farhane et al., 2018; Koba & Konopa, 2005). Actinomycin D has cytotoxic and antineoplastic effects, inducing P53-independent

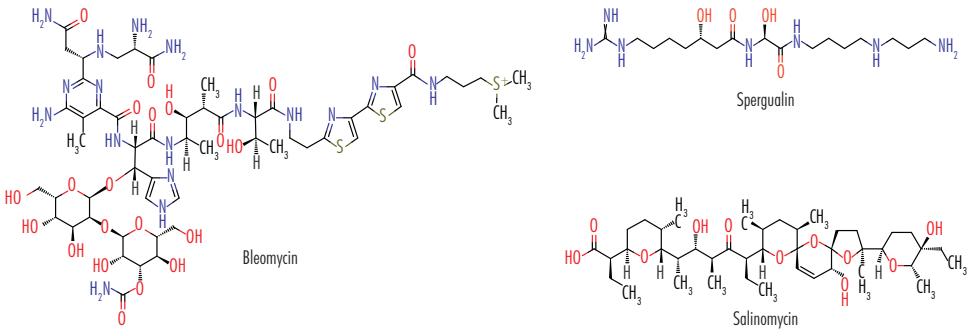


Figure 2. Chemical structures of some members of the peptide class of antibiotics as antimicrobial and antitumor agents, synthesized by microorganisms.

cell apoptosis (Prouvot et al., 2018; Dactinomycine accessed 20 February 2018; Hazel et al.,1983).

*Spergualin* is a water-soluble peptide possessing a special chemical structure: it has a C-terminal guanidyl group and a C-terminal polyamine. It stimulates T-cell-mediated cytotoxic immunity (Umezawa K &Takeuki T, 1987; Umezawa H et al., 1987, Nishikawa et al., 1986).

*Bleomycin*'s molecule consists of a central heptapeptide that represents the binding site of different groups under the action of halogenases and transferases therefore generating a large structural diversity. Bleomycin was discovered by Hamao Umezawa (1962) in *Str. verticillus* cultures filtrates bacterium. All bleomycins have the same general structure, but differ by function group attached to the terminal amino group (ACS - Chemistry for life, 2020). The natural form is a mixture of two glycopeptide antibiotics: Bleomycin A2 and Bleomycin B2, bound with 3 carbohydrate residues. Bleomycin binds DNA and possibly RNA. In the presence of $Fe^{+2}$ forms a *pseudoenzyme* that interacts with $O_2$ resulting in the release of superoxide (*in vitro* $O_2^-$) and $OH^-$ groups that cleave DNA resulting single and double strand breaks (Segerman et al., 2013). Bleomycin sulfate is used to treat Hodgkin and non-Hodgkin lymphoma, squamous cell carcinomas and cancer-related pleural effusion. Some bacterial and tumour cells encode a bleomycin-inactivating hydrolase, which hydrolyses the amide group attached to beta-amino alanine. The protection degree against bleomycin depends on hydrolase level (Sugiyama & Kugamai, 2002; Bayer et al., 1992; Baindara & Mandal, 2020, Latta et al., 2015; Egger et al., 2013).

*Salinomycin* is a monocarboxylic polyether isolated from *Str.albus* (Miyazaki et al., 1974) and is used as an antibacterial, antifungal, antiparasitic and antitumoral drug (Hyun-Gyo Lee et al., 2017, Zhou et al., 2013, Gupta et al., 2009). The polyether skeleton acts as a cationic ionophore, forming complexes with metal cations and interfering with the ion exchange function of the cell membrane. It binds to monovalent cations (Na > K > Cs) and divalent cations (Sr > Ca > Mg), having high affinity for K ions, and interferes with its transmembrane potential. Both *in vivo* and *in vitro*, it induces ROI (extracellular reactive oxygen intermediates) release and apoptosis of leukemic CD4 cells, but not of CD4 cells sampled from healthy individuals (Piperno et al., 2016). Salinomycin is EMT and metastases inhibitor (Chen 2014).

## Quinolones

*Quinolones* (also called 4-quinolones) are a family of molecules that share the quinolinic nucleus. They are the first synthetic antimicrobial agents obtained by synthesis. Changes in the chemical structure of nalidixic acid have given rise to the new generation quinolones or fluoroquinolones

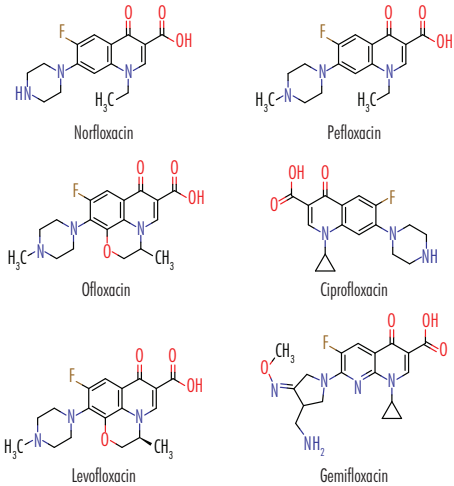


Figure 3. Chemical structures of some members of the quinolone class of antibiotics as antimicrobial and antitumor agents, synthesized by microorganisms.

(norfloxacin, pefloxacin, ofloxacin, ciprofloxacin, levofloxacin etc.) which have an extended antibacterial spectrum. Along with beta-lactams and macrolides, quinolones are one of the most widely used antimicrobial agents used in humans. Quinolones inhibit the DNA gyrase quickly stopping the replicative DNA synthesis. Quinolones are toxic to mammalian cells *in vitro* and *in vivo* experimental models (Goto & Wang 1985; Warren, 1985; Liu, 1989).

Among fluoroquinolones, the most used is ciprofloxacin, which has a wider antibacterial spectrum compared to nalidixic acid. In ciprofloxacin molecule, fluorine ensures activity on Gram-positive bacteria, piperazine group increases anti-enterobacteria activity and piperazine and cyclopropyl groups enable anti-*Pseudomonas* activity. Ciprofloxacin is widely used in the therapy of urinary, respiratory and gastrointestinal infections. It is also active on cell lines from human and animal bladder neoplasia. Ciprofloxacin has anti-proliferative and pro-apoptosis effects, since *gemifloxacin* is EMT (anti- epithelial-mesenchymal transition) and metastases inhibitor (Chen 2014).

## Conclusions

Since the discovery of their antitumor effect, three main classes of antibiotics were used as adjuvants in cancer therapies: anthracyclines, peptide antibiotics and quinolones. They have both antimicrobial and antitumoral activity, being able to induce DNA breaks and to inhibit DNA and RNA synthesis and protein synthesis. Through these mechanisms, the antitumor antibiotics inhibit EMT and metastases formation (salinomycin, gemifloxacin), induce P53-independent cell apoptosis, stimulate T-cell-mediated cytotoxic immunity, thus exhibiting anti-proliferative and pro-apoptosis effects.

## Conflict of interest

The authors declare that they have no conflict of interest.

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