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Review

Drug Repurposing of Selected Antibiotics: An Emerging Approach in Cancer Drug Discovery

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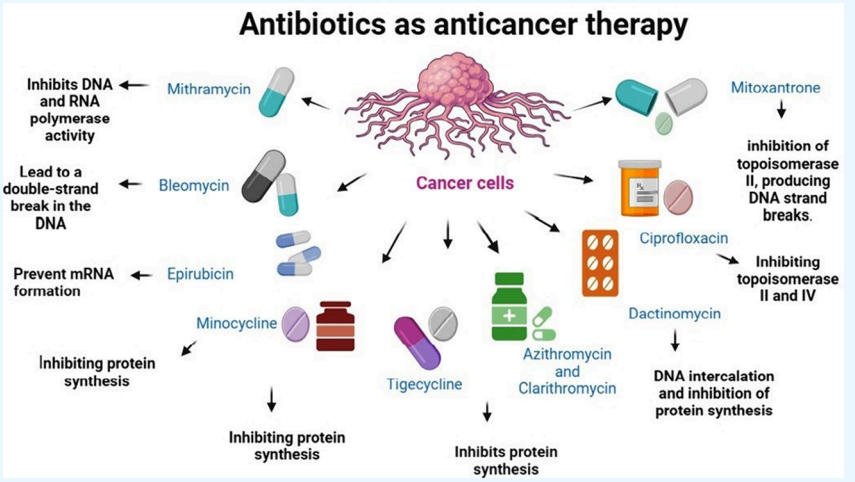

ABSTRACT: Drug repurposing is a method of investigating new therapeutic applications for previously approved medications. This repurposing approach to "old" medications is now highly efficient, simple to arrange, and cost-effective and poses little risk of failure in treating a variety of disorders, including cancer. Drug repurposing for cancer therapy is currently a key topic of study. It is a way of exploring recent therapeutic applications for already-existing drugs. Theoretically, the repurposing strategy has various advantages over the recognized challenges of creating new molecular entities, including being faster, safer, easier, and less expensive. In the real world, several medications have been repurposed, including aspirin, metformin, and chloroquine. However, doctors and scientists address numerous challenges when repurposing drugs, such as the fact that most drugs are not cost-effective and are resistant to bacteria. So the goal of this review is to gather information regarding repurposing pharmaceuticals to make them more cost-effective and harder for bacteria to resist. Cancer patients are more susceptible to bacterial infections. Due to their weak immune systems, antibiotics help protect them from a variety of infectious diseases. Although antibiotics are not immune boosters, they do benefit the defense system by killing bacteria and slowing the growth of cancer cells. Their use also increases the therapeutic efficacy and helps avoid recurrence. Of late, antibiotics have been repurposed as potent anticancer agents because of the evolutionary relationship between the prokaryotic genome and mitochondrial DNA of eukaryotes. Anticancer antibiotics that prevent cancer cells from growing by interfering with their DNA and blocking growth of promoters, which include anthracyclines, daunorubicin, epirubicin, mitoxantrone, doxorubicin, and idarubicin, are another type of FDA-approved antibiotics used to treat cancer. According to the endosymbiotic hypothesis, prokaryotes and eukaryotes are thought to have an evolutionary relationship. Hence, in this study, we are trying to explore antibiotics that are necessary for treating diseases, including cancer, helping people reduce deaths associated with various infections, and substantially extending people's life expectancy and quality of life.

INTRODUCTION

Cancer is a common and often-seen disease that poses a serious health risk to people. Cancer is caused by abnormal cells growing out of control and the genome changing quickly (which causes cancerous features in normal cells).[1] In 2020, there was an estimate of 19 million new cases of cancer and nearly 10 million deaths due to cancer.[2] Cancer's basic cause is the aberrant cell growth and motility caused by an unregulated

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cell cycle and the constant cancer stem cell self-renewal and reproduction.[3] The spread of cancer interferes with typical biological processes, including those of healthy cells. This is completed by infiltrating and spreading to adjacent tissues.[4] Usually, cancer therapies include radiation therapy, chemotherapy, surgery, laser therapy, and combination therapy. Selective treatments have been found to improve the knowledge of the biology and molecular genetics of cancer progression and metastasis at the same time.[5] 90% of chemotherapy failures during cancer spread and invasion are due to drug resistance. During chemotherapy, a lot of the patient's tumor cells stop responding to the drug. In the field of cancer, drug resistance seems to be a big problem[6] (Figure 1).

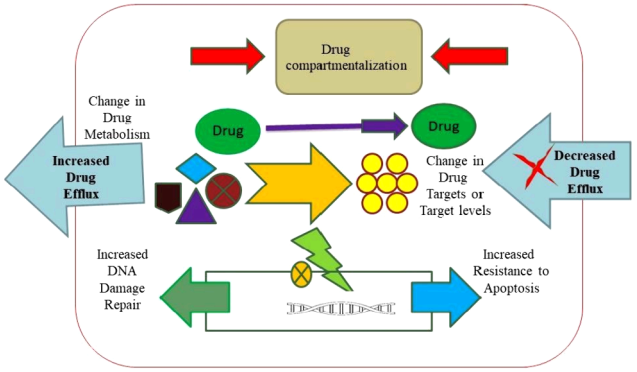

Figure 1. Drug resistance in cancer cells can occur through a variety of mechanisms, including drug inactivation, multidrug resistance, cell death inhibition (apoptosis suppression), modifications to drug metabolism, modifications to drug targets, improved DNA repair, and target gene amplification.

DRUG RESISTANCE

Anticancer drug resistance is a complicated process that begins when the drug targets change. New approaches to treating drug resistance have been made possible by developments in DNA microarrays and proteomics and the creation of targeted therapies. Even though the designs of new chemotherapy drugs are improving significantly, there is still no chemotherapy drug that can effectively treat advanced cancers (such as invasion and metastasis). Many mechanisms can make cancer cells resistant to anticancer drugs, like genetic differences, increased drug efflux, alterations in drug targets, activation of alternative signaling pathways, enhanced DNA repair mechanisms, multidrug resistance process, inhibiting apoptosis, and epigenetic changes. Potentially new therapeutic substances are discovered by the method of drug discovery, which incorporates computational, exploratory, translational, and clinical studies.[7] Drug discovery is still a drawn-out, costly, challenging, and ineffective method with an elevated loss of new therapeutic discovery, despite advances in the field of biotechnology and our understanding of biological systems. Drug design is the systematic procedure of generating novel pharmaceuticals or treatments through the identification and development of molecules that possess the ability to selectively engage with particular biological targets within the body, with the aim of treating or preventing diseases. Target identification, Target validation, Lead optimization, Preclinical evaluation, and Clinical development are all steps in the process of developing new drugs. Modern drug discovery involves determining screening hits and medicinal chemistry and improving those approaches to increase affinity, selectivity (to reduce the possibility of side effects), efficacy or potency, stability in metabolism (to prolong the half-life), and oral absorption. When a compound has been identified that satisfies all of those criteria, the method to create a drug begins before clinical evaluation is carried out. Antibiotics are chemicals that prevent bacteria from multiplying. They are developed biologically or by natural processes and function by either eliminating or hindering the growth of bacteria. The use of antibiotics has not only inhibited infections but also made it possible to treat them, enabling open-heart surgery, cancer treatment, or organ transplantation. The post-antibiotic era has compelled policy makers to recognize these risks to human health and declare extra funding, which is gradually restoring attention to antibiotic discovery and development.[8] Antibiotics are necessary for treating disease, helping people reduce deaths associated with various infections, and substantially extending people's life expectancy and quality of life. Scientists have discovered that they also inhibit the growth of eukaryotic cells, which may be related to their common evolutionary link with prokaryotes. The vital impact of antibiotics on human beings led to the thought of testing them against cancer cells as the work of drug discovery is very challenging and demanding.

CANCER ANTIBIOTICS AND THEIR ROLE IN CANCER PROGRESSION AND INHIBITION

In cancer, some of the antibiotics play an important role as cancer antibiotics. These cancer antibiotics are some of the most significant forms of antibiotics. These antitumor antibiotics primarily function via the following mechanisms: (i) the pro-apoptotic effect; (ii) the antiproliferative effect; and (iii) anti-epithelial-mesenchymal transition (EMT) inhibition.[9] Anticancer, or antitumor, antibiotics are a type of drug that stops cell growth by interfering with the genetic material of cells. Anticancer antibiotics are mostly made of anthraquinones and peptides that stop cancer cells from multiplying and growing out of control. Antibiotics that kill cancer cells include bleomycin, dactinomycin, mitomycin, and enediyne.[10] Antibiotics have different modes of action as anticancer agents. Usually, they interfere with DNA and RNA function by intercalating with it and binding to the DNA. For example, doxorubicin is used to treat breast, ovarian, and lung cancer, soft tissue sarcoma, Wilms tumor, and neuroblastoma cancer.[11] It is a broad-spectrum antibiotic that appears to be an effective anticancer agent. Mitomycin is used for bladder cancer,[12] daunorubicin is used for acute myeloid leukemia and acute lymphoblastic leukemia (ALL),[13] idarubicin is used for chronic myeloid leukemia and acute myeloid leukemia,[14] epirubicin is used for breast and gastroesophageal cancer,[15] and mitoxantrone is used for hormone-refractory prostate cancer.[16] Aclarubicin is less harmful to the heart. In addition, another productive antibiotic that has low cardiotoxicity is pirarubicin. It is a particularly lipophilic molecule; thus, the absorption rate is considerably elevated. Aclarubicin is currently being tested in phase III trials for severe leukemias, lymphoma, or breast cancer.[17,18] In the cases of breast cancer and leukemia, zorubicin is a more potent chemotherapy antibiotic. An antibiotic called valrubicin is used in the treatment of bladder cancer when Bacillus Calmette-Guerin (BCG) therapies are ineffective.[19] Pixantrone is similar to mitoxantrone. Additionally, it is in a phase III trial and has minimal cardiotoxicity. It is used to treat aggressive NHL (non-Hodgkin lymphoma),

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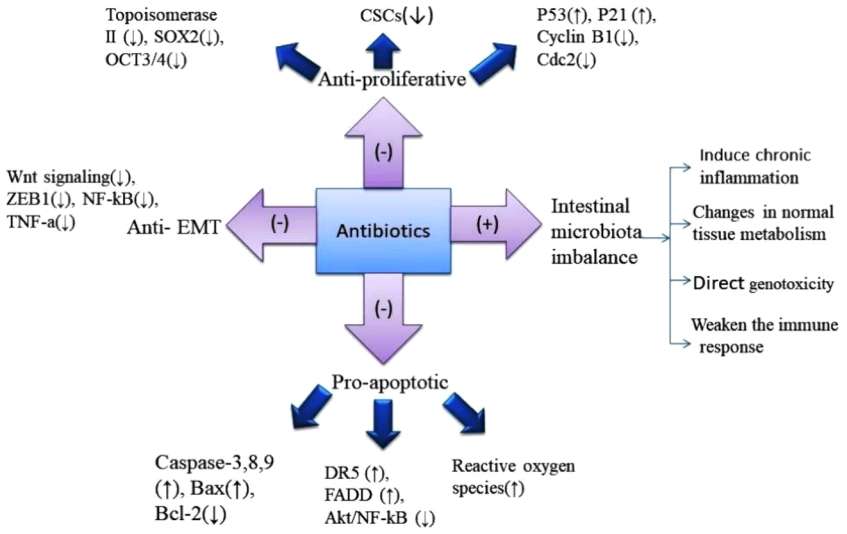

Figure 2. Antibiotics exert their anticancer effects by different mechanisms. Pro-cancer (+), anti-cancer (−), up-regulated (↑), and down-regulated.

which is cancer of the lymph tissue.[20] The cell cycle is modified in such a way as to produce an antiproliferative effect. Antibiotics can affect the entire growth cycle, including the G0 phase. Cyclinenone-specific drugs are an example.[21] Salinomycin is an antibiotic that induces cell death.[22] Salinomycin inhibited TGF-induced EMT and cell migration in non-small cell lung cancer (NSCLC) cell lines.[23] Figure 2.

CLASSIFICATION OF ANTIBIOTICS AND THEIR VARIOUS ROLES IN CANCER

Antibiotics can be classified in several ways, but the most popular classification systems are based on molecular features, modes of action, and spectrums of activity. Some common classes of antibiotics based on chemical or molecular structures include beta-lactams, macrolides, tetracycline, quinolones, aminoglycosides, sulfonamides, glycopeptides, and oxazolidinones (Figure 3 and Table 1).

In the 20th century, science and technology developed quickly, especially biomedicines. One of the most important types of antibiotics is the anticancer class, which has its own way of stopping cancers from growing.[36] It can be shown that

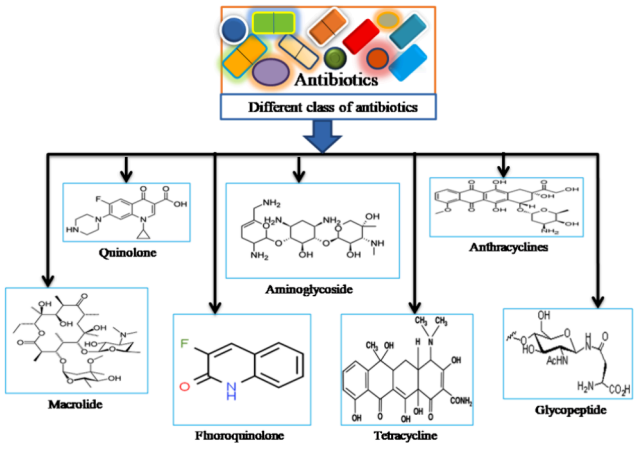

Figure 3. Chemical structures of various antibiotic classes: (a) quinolone; (b) aminoglycoside; (c) anthracyclines; (d) macrolide; (e) fluoroquinolone; (f) tetracycline; (g) glycopeptide.

anticancer antibiotics work against cancer primarily through three mechanisms: anti-epithelial mesenchymal transition (EMT), pro-apoptotic, and anti-proliferative.

In addition, anticancer antibiotics can eliminate cancer cells at every stage of the cell cycle, including G0 cells. Specifically, cyclinenon-specific treatments (CCNSC) and similar agents interfere with the cell cycle to prevent the proliferation of cancer cells.[21] Conversely, anticancer antibiotics might encourage cancerous cell deaths by emphasizing the apoptotic genes B cell lymphoma-2 (Bcl-2), apoptosis-inducing pro-Bcl-2-associated x (Bax), caspase-3, caspase-8, and caspase-9 and the cancer-suppressor P53 gene. This influences patient-specific cancer cell death.[22] Anticancer antibiotics can also be employed as EMT inhibitors to prevent cancer cells from spreading and have a role in cancer prevention.[23] Ciprofloxacin, for example, can induce apoptosis, whereas salinomycin can inhibit cancer cell proliferation and prevent epithelial-mesenchymal transition (EMT).[37] Some known anticancer antibiotics play an important role in cancer treatment and progression (Figure 4).

(i). Plicamycin. Mithramycin (MTM), also known as Plicamycin, is a non-anthracycline antitumor antibiotic. The three effective groups are made up of the structures of benzoquinone and ethylene imine,[9,38] and it has been approved as a natural product to treat hypercalcemia and has also shown good antitumor effects when used to treat testicular embryonal cancer, glioblastoma, and Ewing sarcoma.[39] It can also be used to treat glioma, lymphoma, and other cancers,[40] and it works in both acidic and hypoxic conditions. It works by attaching to GC-rich DNA sequences, which is the basis of its mechanism of action, which inhibits SP family transcription factors from binding to gene promoters.[41] Since c-Myc was shown to control the expression of CD47 and PD-L1, mithramycin (MIT), a common c-Myc inhibitor, was used. However, no one knows how mithramycin (MIT) affects immunological checkpoint molecules.[42] It was revealed that pan-tissue microarray cancer had higher CD47 expression. In cancer cells, SK-MEL-28 or B16 CD47 proteins and mRNA expression levels were decreased by mithramycin (MIT). Mithramycin blocked the surface expression of CD47-stimulated THP-1 cell phagocytosis in the SK-MEL-28 cells. Mithramycin increased the expression of PD-L1 in cancer,

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Table 1. Classification of Antibiotics According to Mode of Action

S.No.	Class name	Antibiotics name	Mode of action	Refs
1.	Anthracyclin	(a) Daunorubicin (b) Doxorubicin (c) Epirubicin (d) Idarubicin (e) Mitoxantrone (f) Valrubicin (g) Aclarubicin (h) Pirarubicin	Cytostatics and harmful actions of anthracyclines include free radical creation, peroxidation of lipids, govern membrane effects, and enzyme interactions.	24
2.	Non Anthracyclin	(a) Mitomycins (b) Bleomycins (c) Pingyangmycin (d) Actinomycins (e) Mithramycin	Including the production of free radicals, lipid peroxidation, immediate effects on the membrane, and enzyme interactions.	9
3.	Tetracycline	(a) Chlortetracycline (b) Oxytetracycline (c) Demeclocycline (d) Lymecycline (e) Methacycline (f) Minocycline (g) Rolitetracycline (h) Doxycycline or Tigecycline	It makes use of ribosomes, which are responsible for converting an mRNA code into useful proteins.	25
4.	Fluoroquinolones	(a) Ciprofloxacin (b) Delafloxacin (c) Gemifloxacin (d) Levofloxacin (e) Moxifloxacin (f) Norfloxacin (g) Ofloxacin	Fluoroquinolones act by inhibiting two enzymes involved in bacterial DNA synthesis, both of which are DNA topoisomerases that human cells lack and that are essential for bacterial DNA replication, thereby enabling these agents to be both specific and bactericidal.	26
5.	Quinolone	(a) Nalidixic acid (b) Enoxacin (c) Norfloxacin (d) Ciprofloxacin (e) Ofloxacin (f) Lomefloxacin (g) Sparfloxacin (h) Grepafloxacin (i) Clinafloxacin (j) Gatifloxacin (k) Moxifloxacin (l) Gemifloxacin (m) Trovafloxacin (n) Garenoxacin	Quinolones act by converting their targets, gyrase and topoisomerase IV, into toxic enzymes that fragment the bacterial chromosome.	27
6.	Macrolide	(a) Erythromycin (b) Azithromycin (c) Clarithromycin (d) Dirithromycin (e) Roxithromycin (f) Flurithromycin (g) Josamycin (h) Rokitamycin (i) Kitasamycin (j) Mirosamycin (k) Oleandomycin (l) Rosaramicin (m) Spiramycin (n) Tylosin	Macrolides revolve around their ability to bind the bacterial 50S ribosomal subunit causing the cessation of bacterial protein synthesis.	28
7.	Glycopeptide	(a) Vancomycin (b) Teicoplanin (c) Ramoplanin (d) Oritavancin	Glycopeptides inhibit the synthesis of cell wall peptidoglycan and inhibit bacterial cell membrane permeability.	29

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Table 1. continued

S.No.	Class name	Antibiotics name	Mode of action	Refs
		(e) Dalbavancin		
		(f) Telavancin		
8.	Aminoglycosides	(a) Neomycin (b) Kanamycin (c) Gentamicin (d) Netilmicin (e) Tobramycin (f) Amikacin (g) Plazomicin (h) Arbekacin (i) Apramycin	Aminoglycosides inhibit protein synthesis by binding, with high affinity, to the A-site on the 16S rRNA of the 30S ribosome.	30
9.	Sulphonamides	(a) Mafenide (b) Sulfacetamide (c) Sulfadiazine (d) Sulfadoxine (e) Sulfamethizole (f) Sulfa met (g) Hoxazole (h) Sulfanilamide (i) Sulfasalazine	A sulfonamide interferes with the ability of bacteria to use folic acid to grow by stopping the metabolic process.	31
10.	Beta-Lactam	(a) Penicillins (b) Cephalosporins (c) Carbapenems (d) Monobactams	The beta-lactam antibiotics inhibit the last step in peptidoglycan synthesis by acylating the transpeptidase involved in cross-linking peptides to form peptidoglycan.	32
11.	Carbapenems	(a) Doripenem (b) Ertapenem (c) Imipenem (d) Meropenem	Carbapenems work by penetrating the cell wall of bacteria, binding with penicillin-binding proteins (PBPs), and inactivating intracellular autolytic inhibitor enzymes, ultimately killing the bacterial cell.	33
12.	Cephalosporins	(a) Cefadroxil (b) Cefazolin (c) Cephalexin (d) Cefaclor (e) Cefotetan (f) Cefoxitin (g) Cefprozil (h) Cefuroxime (i) Cefotaxime (j) Ceftazidime (k) Cefdinir (l) Ceftriaxone (m) Cefpodoxime (n) Cefoperazone (o) Cefixime (p) Cefepime	Bacteria synthesize a cell wall that is strengthened by cross-linking peptidoglycan units via penicillin-binding proteins (PBPs, peptidoglycan transpeptidase).	34
13.	Chloramphenicol	(a) Chloromycetin (b) Chloroptic (c) Fenicol (d) IsoptoFenicol (e) Chloramphenicol (f) Ophtho-Chloram (g) Pentamycetin	Chloramphenicol inhibits protein synthesis by binding to the 50S ribosomal subunit and directly preventing the formation of bacterial protein.	35

potentially by inhibiting PD-L1 from being ubiquitinated and by making ROS and IFN levels higher. Using an immune checkpoint array, we found that MIT stopped FasL and Galectin3 from being made. According to this research, mithramycin inhibits CD47 interpretation while enhancing PD-L1 expression.[42] Also, when mithramycin (MIT) and anti-PD-1 antibodies are used together, they have a strong effect against cancer. Also, the addition of oxygen radicals caused by MMC could help fight cancer.[43] This drug's bad side effect is bone marrow suppression, which shows up mostly as very few platelets.

(ii). Bleomycin. An antibiotic called bleomycin (BLM) is produced by the bacterium *Streptomyces verticillus*.[44] It has been used as an anticancer chemotherapeutic drug to treat diseases that can be cured, like germinative tumors and Hodgkin's lymphoma, including squamous cell carcinoma, and

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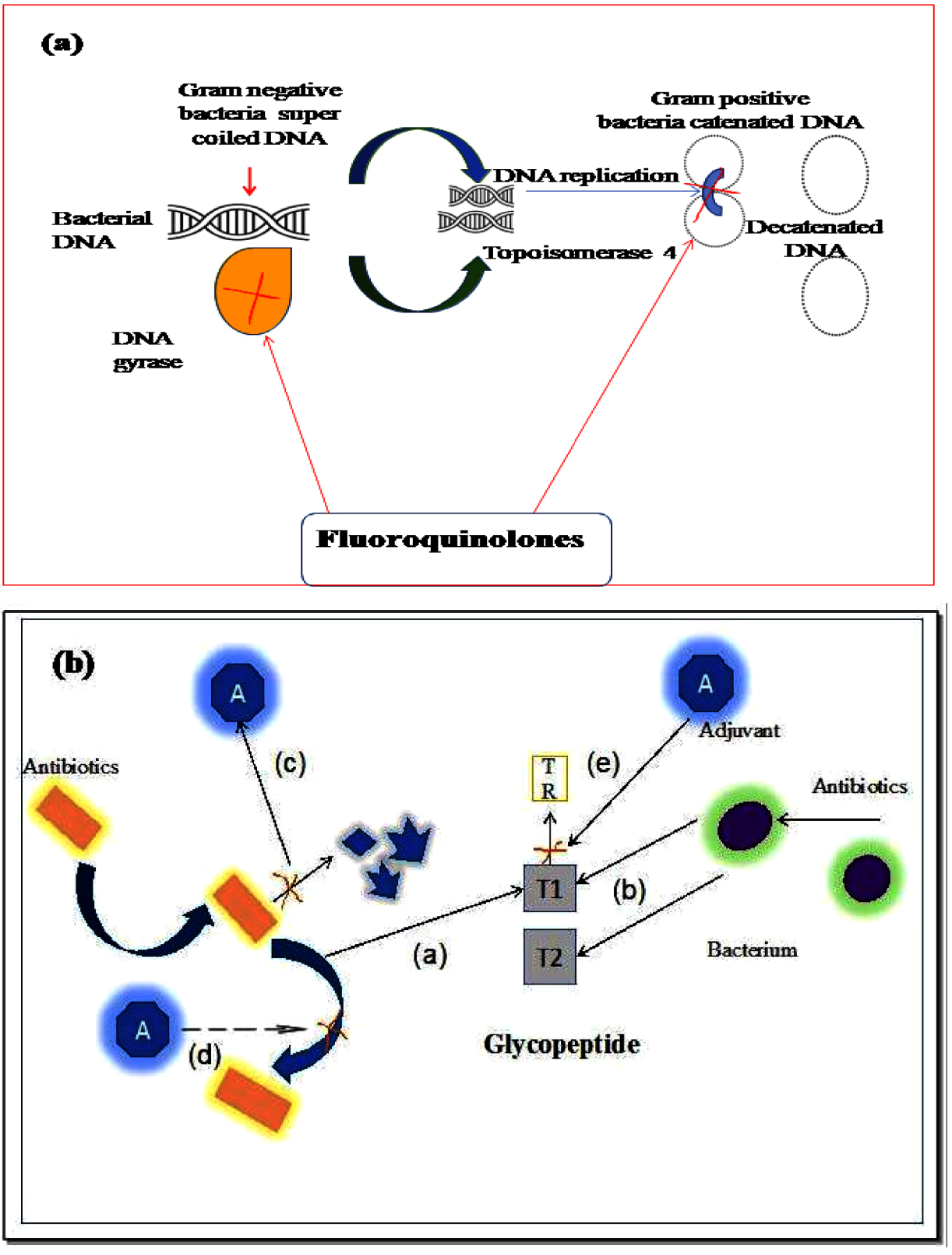

Figure 4. continued

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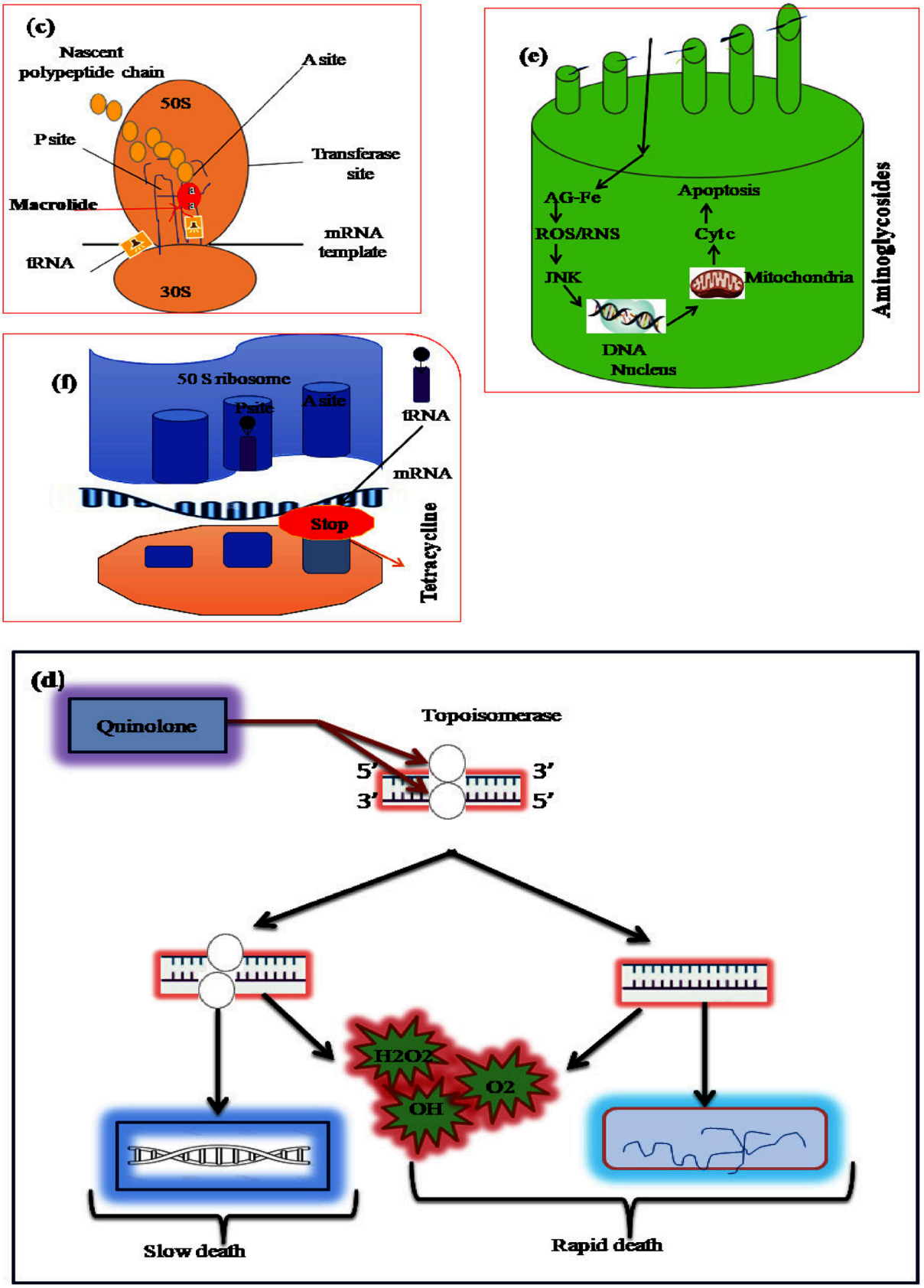

Figure 4. Different anticancer antibiotics and their modes of action: (a) Fluoroquinolone DNA gyrase inhibition inhibits the supercoiling of bacterial DNA in Gram-negative bacteria, while topoisomerase IV inhibition prevents the segregation of replicated DNA in Gram-positive bacteria; (b) Glycopeptide that inhibits the late stages of peptidoglycan synthesis; (c) Macrolide protein synthesis inhibitor; (d) Quinolone inhibits the catalytic activity of DNA gyrase and topoisomerase IV; (e) Aminoglycosides bind to the 16S rRNA of the 30S subunit and inhibit protein synthesis; (f) Tetracycline's action prevents the addition of further amino acids to the nascent peptide.

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induced pulmonary fibrosis.[45,46] Through its amino-terminal peptide, it can bind to DNA, and when oxygen and iron are present, by stimulating a DNA-Fe-bleomycin complex, it forms free hydroxyl radicals.[47] It can affect both single- and double-stranded DNA, stopping DNA synthesis, preventing cancer cells from growing, and inducing apoptosis. BLM is cytotoxic because it oxidizes thymidylate and other nucleotides in deoxyribose. This results in single- and double-stranded DNA breaks, chromosomal abnormalities, gaps, degradation, and translocation. BLM has antitumor action in various cancers, including head and neck, cervix, and vulva cancers.[48,49] Smad2 (ser465/467) and Smad3 (ser423/425) were phosphorylated complexes, with accumulating Smad4 in the nucleus controlling the transcription of target genes as a result of the stimulation of phosphorylation of these activated TGF-β receptors.[50,51] The aberrant expression of Smad4 is one proposed mechanism for the loss of the tumor suppressor function of the Smad signaling pathway or interference with Smad4 activation.[52] BLM controls the Smad signaling pathway, which inhibits the invasive biological characteristics of MKN45 and AGS cells and, hence, has a suppressive effect on gastric cancer growth and progression.

(iii). Daunorubicin. Daunorubicin is an antibiotic in the class called anthracyclines. It works against cancerous growth in many ways, including by stopping cells from dividing and killing cells. *Streptomyces coeruleorubidus* or *S. peucetius* bacteria naturally produce it. A first-line cancer antibiotic known as daunorubicin is frequently used to treat acute myelogenous leukemia, lymphocytic leukemia, and other types of solid tumors.[53] The topoisomerase II enzyme is inhibited through the intercalation of DNA base pairs, which causes the uncoiling of the DNA double helix and leads to single- and double-strand breaks, which prevent the production of DNA and RNA. Apoptosis, mitochondrial damage, and programmed cell death are all caused by the daunorubicin inhibition of the polymerase enzyme activity, which also disrupts the regulation of gene expression. It can stop the growth of cancer by strongly adhering to DNA and chimerism with the DNA base pairs of cancer cells, obstructing the spatial configuration of DNA.[54] Breast cancer, lymphoma, and acute leukemia are the main conditions under which daunorubicin is used. AIDS-related Kaposi sarcoma and multiple myeloma have both been treated with doxorubicin and daunorubicin liposomal formulations.[55] The medication has a terminal half-life ($t_{1/2}$) of 15−18 h, a high degree of 13-dihydro derivative metabolization, and a mostly hepatic and 10% renal route of elimination. According to ref 56, several daunorubicin derivatives have been created, and these compounds display potent cytotoxicity against tumor cells through a variety of mechanisms, including inhibition of topoisomerase II.

(iv). Epirubicin. Epirubicin (Epi), an anthracyclines antibiotic, has a constrained clinical use.[55] Epirubicin is a nonspecific cell cycle inhibitor that seems to be effective against a different variety of transplant cancers. Ovarian cancer, colon cancer, soft tissue sarcoma, lung cancer, stomach cancer, malignant melanoma, and others are among the many tumors for which epirubicin, a novel anthracyclines antibiotic, is commonly used as treatment.[56,57] It can be located between DNA base pairs to reduce transcription and inhibit mRNA synthesis, thereby blocking the synthesis of DNA and RNA.[58] Due to its cardiotoxicity and bone marrow suppression, an epirubicin-modified polyvalent aptamers system (MPAS) compound was developed in the present research to treat colon carcinoma cells (C26) and murine breast cancer cells (MCF-7) to distribute the implications of epirubicin on C26 and MCF-7 cells, and a modified and promoted epirubicin-MPAS conjugate was created by combining two types of aptamers (target cells). Chemotherapeutic agents may be more effective and have minimal side effects if they are delivered in a more targeted manner because DNA dendrimers can hold a lot of drugs and are very stable, These DNA nanostructures are one-of-a-kind applicants for genetic application. Aptamers are classified into three types (MUC1, AS1411, and ATP) and will be used in this study to modify and promote dendrimers that would deliver epirubicin to specific cells. In the breast cancer cells (MCF-7) and C26, its effectiveness was assessed (murine colon carcinoma cell). Epirubicin complex, Apts-dendrimer, and Apts-dendrimer conjugates were given to C26 cells, and MCF-7 and not target Chinese hamster ovary cells are used in the MTT assay (cytotoxic study). Flow cytometry analysis was used to measure the internalization. At last, the complex was used to stop the growth of tumors in living cells; 25 lM epirubicin was added to 1 lM dendrimer effectively. Epirubicin got out of the epirubicin complex, Apts-dendrimer, in a way that depended on the pH (more release at pH 5.5). In comparison to epirubicin alone, the Apts-dendrimer-epirubicin combination was less cytotoxic in CHO cells. In MCF-7 cells and C26, the combination was more cytotoxic than epirubicin alone. The Apts-dendrimer-epirubicin complex may also successfully inhibit tumor growth in vivo. pH-sensitive epirubicin release, effective epirubicin loading, and tumor targeting were all characteristics of this combination. These attributes make it possible for the proposed drug delivery process to also prevent epirubicin side effects while improving therapeutic potential.[58]

(v). Doxycycline. A wide-spectrum tetracycline derivative antibiotic was initially approved by the Food and Drug Administration (FDA) in the late 1960s. Tetracyclines prevent activating aminoacyl-tRNAs from binding near the production of proteins, and this can therefore be prevented by restricting the A-site of the bacteria's ribosomal 30S subunit.[59] Since mitochondrial biogenesis plays an essential role in CSC survival and anchorage-independent development of clones, it is known that cancers in the breast develop from breast cancer stem cells (BCSCs), according to experimental data. As a result, mitochondria are an important therapeutic target. Doxycycline, an antibiotic, inhibits mitochondrial biogenesis.[60,61] Doxycycline stops breast cancer cells and BCSCs from doing things like making the mammosphere, apoptosis, migrating, expressing stem cell markers, invading, and going through the epithelial-mesenchymal transition (EMT). Also, if autophagy is involved in how doxycycline stops breast cancer cells from growing, it has also been proven that doxycycline therapies significantly lowered Oct4, Sox2, Nanog, and CD44 appearance. Further evidence suggests that doxycycline, with its ability to downregulate the autophagy of the LC-3BI and LC-3BII markers, may play a role in the new effects on stem cell markers and EMT proliferation. The treatment with doxycycline stopped breast cancer and cancer stem cell-like properties, demonstrating that this antibiotic has the potential to be applied as an anticancer agent for patients in a clinical setting.[62,63] Cancer stem cells, also known as CSCs, play an important role in cancer development and propagation.[64] Because protease activation receptor 1 (PAR1) was already

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associated with tumor recurrence, no research has been carried out to evaluate PAR1's role in the emergence of pancreatic cancer stem cells (CSCs). PAR1 was assessed to see how it affected the production of CSCs, like pancreatic cancer cells, which already have specifications similar to those of cancer stem cells. PAR1 overexpression in Aspc-1 cells has been shown to produce CSC-like traits, but PAR1 interaction in Panc-1 cells had the opposite effect. Excessive PAR1 appearance and protein focal adhesion kinase (FAK) also have a significant effect on patients' diagnose and treatment outcomes. The PAR1/FAK/PI3K/AKT pathway is blocked by doxycycline, which also enhances the therapeutic effect of 5-FU.[65] Doxycycline strongly reduced the number of ALDH+ BCSCs as well as the efficacy of mammosphere initiation in the HER2+ and triple-negative breast cancer (TNBC) subsets. Furthermore, the paclitaxel-induced improvement of ALDH+ BCSCs in TNBC was decreased by doxycycline. Researchers suggest that it should be safe to use in combination with chemotherapeutic drugs to kill both CSCs and bulk tumor cells.[66]

(vi). Minocycline. The second-generation antibiotic known as minocycline (7-dimethylamino-6-desoxytetracycline) is frequently used in medical procedures. It has a long history of being safe as an antibacterial and anti-inflammatory drug.[67] It has several non-antimicrobial qualities in addition to its anticancer activity.[68] Regardless of common knowledge of the disease, studies on cancers of the ovaries, cancers of the liver, glioma cells, and acute myeloid leukemia cells confirmed the anticancer effect, and malignant melanoma goes on to be a serious medical issue.[69] Primary treatment ineffectiveness, combined with treatment resistance, results in a high death rate. Researchers carried out the study using the COLO 829 human skin cancer cell line. By drug dosage, minocycline decreased cell viability and eliminated skin cancer growth and incubation duration, according to the findings. Furthermore, minocycline decreased mitochondrial membrane potential, while increasing cells with low levels of reduced glutathione. Human melanoma cells were treated, which reduced proliferation, disrupted the cell cycle, and dramatically altered cell shape.[70] The outcome of the experiment indicated that the minimum concentration of the drug possessed a cytostatic effect, although concentrations of 100 and 200 M minocycline appear to be more cytotoxic. Additionally, minocycline anti-melanoma activity is connected to apoptosis induction. Minocycline appears to be a substance with promising and effective anticancer abilities that can be used to treat a variety of present melanoma treatment problems.[71] Minocycline inhibits the STAT3 and ERK1/2 signaling pathways and downregulates two important mechanisms of the IL-6 receptor process.[72] Minocycline's functional role in metastatic activity was revealed by its ability to block cellular motility, invasion, and adhesion, which was linked to the loss of regulation of MMP-9 and MMP-2 (matrix metalloproteinases).[73] Studies have shown that minocycline may play a role in lowering IL-6 expression and activity. When minocycline is consequently clinically tested for ovarian cancer, these side effects can be important. Minocycline also prevents cellular metastatic activity in the cell culture, including adhesion, invasion, and migration. Further research is needed to determine first if minocycline can be used to treat ovarian cancer as well as other IL-6-dependent cancers.[74] According to research results, accompanied by minocycline clinical utilization, it is a potential antibiotic for use and possibly clinical research in the treatment of ovarian cancer due to its three decades of use, safety, bioavailability, and cost-effectiveness.[75]

(vii). Tigecycline. Tigecycline is an antibiotic of the glycylcycline class that is structurally similar to tetracyclines. It inhibits protein translation by strongly attaching to the 30S ribosomal subunit, limiting charged aminoacyl-tRNAs from entering the A-site of the ribosome during bacterial translation, and thereby inhibiting peptide elongation.[76] Tigecycline is a potent anticancer drug that is safe and well-tolerated for the treatment of complex infections.[77] Tigecycline targets cancerous cells in tumor environments while preserving the activity of healthy cells.[78] Furthermore, tigecycline (TIG) adheres to the advised tolerability profile for chemotherapy drugs and seems to go above and beyond the necessary safety regulations. Additionally, tigecycline may be used as a supplement to therapy for cancers like breast, prostate, chronic myeloid leukemia, and gastric cancer.[79,80] Additionally, Lu et al. (2017) have shown that tigecycline has anti-acute myeloid leukemia (AML) activity in vitro and in vivo.[81] Because it inhibits mitochondrial translation, Wnt/-catenin activation, and autophagy activation, this antibiotic has drawn interest as a potential anticancer treatment.[49] The primary cell cultures of chronic myelogenous leukemia (CML), including those that were drug-resistant, were inhibited by tigecycline from surviving. The inhibition of mitochondrial biogenesis, which removes both cancer cells and cancer stem cells,[59] and the disruption of cell metabolism, which causes apoptosis, were responsible for this. Furthermore, by inhibition of the PI3K-AKT-mTOR pathway, tigecycline induces autophagy. Furthermore, when tigecycline was combined with autophagy suppression, its antileukemic activity increased.[82] It was discovered that tigecycline's anti-leukemic effect is selective. Due to differences in mitochondrial biogenesis, the drug affected only leukemic cells, ignoring normal cells. Tigecycline inhibited the mitochondrial activities and catabolism of CML cells, which led to apoptosis by activating the cytochrome-c and caspase-3 and caspase-9 pathways. Additionally, the combination of tigecycline and an autophagy inhibitor may further enhance this anticancer effect, because tigecycline induces autophagy by inhibiting the PI3K-mTOR pathway. To combat drug resistance in the treatment of CML, combining the use of tigecycline with autophagy inhibition may be a novel strategy.[83]

(viii). Mitoxantrone. Solid tumors, leukemia, and lymphoma are all treated with the synthetic antibiotic mitoxantrone.[84] There have been many investigations into how mitoxantrone interacts with DNA, and all of them point to the drug's biological action being mediated by intercalation into DNA double strands.[85] Mitoxantrone is a topoisomerase II inhibitor.[86] Due to the loss of amino sugar structures, it is less adverse to the heart, does not generate free radicals, and inhibits reactive oxygen species (ROS).[87] However, mitoxantrone can enter cells and connect to cell membranes, preventing cancer from spreading. As a result of cancer progression through mTOR signaling pathways, breast cancer is already presumed to be one of the most dangerous cancers in women.[88] Clinical trials for rapalogs, which are mTOR inhibitors, have shown promise as anticancer drugs, but rapalog resistance is still a problem that needs to be resolved. Therefore, understanding how cells develop rapalog resistance could assist researchers in developing an effective cancer treatment that specifically targets the mTOR protein. According to research reported in ref 89, eEF-2K, which is

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highly expressed in cancer cells and necessary for stressed cells to survive, has been linked to the important regulation of Akt and the beginning of cell-protective autophagy in breast cancer cells as a consequence of mTOR inhibitors. In consequence, by simultaneously inhibiting the two important resistance signaling pathways, eEF-2K inhibition increases the rapalog sensitivity of breast cancer cells. Significantly, researchers used a structure-based computational approach to improve the anticancer agent mitoxantrone, which is required for the treatment of several tumors, as a potential eEF-2K inhibitor.[90,91] According to Guan et al. (2020), mitoxantrone should be combined with an eEF-2K inhibitor to enhance mTOR-targeted cancer treatment because eEF-2K is essential for the signal transduction that leads to the mTOR inhibitor-induced cell-protective autophagy process in breast cancer cells.[92,93]

(ix). Gemifloxacin. The fluoroquinolone antibiotic called gemifloxacin (GMF) stops bacteria from making DNA gyrase and topoisomerase IV. This has antiproliferative and pro-apoptotic effects and also stops cancer from spreading. There have been reports that fluoroquinolones slow down tumor growth, and the cell cycle's G2/M and S phases have been interrupted during DNA synthesis.[94] The movement of cells was a method to evaluate GMF's anti-metastasis capability and invasion, and human breast carcinoma cell lines were used for tissue treatments (MDA-MB-453 and MDA-MB-231). They were assessed in terms of how GMF affected the MET and the NF-kB/Snail pathway that controls them. Thus, according to Chen et al. (2014), GMF stimulated MET, considering that it prevented the invasion and migration of MDA-MB-231 and MDA-MB-453 cells.[95] According to numerous reports, in tumor cells, repeatedly activated nuclear factor B (NF-B) plays an important oncogenic role in influencing malignancy transformation and tumor growth.[95] GMF inhibited TNF-induced cells' migration and invasion, as well as NF-κB activation (TNF-B). GMF prevented NF-κB/Snail from translocations and the inhibitor of B (IκB) from being phosphorylated in both cancer cell types. Consequently, the GMF therapy, a RAF kinase inhibitor protein (RKIP) that prevents IB kinase, is reactivated. RKIP was significantly decreased by small-hairpin RNA transfection. GMF inhibits the NF-KB/Snail pathway as well as cell invasion and migration. The epithelial-mesenchymal transition (EMT) is caused by the snail's inhibition of E-cadherin activity and is triggered by binding to E2-box-like regions within its gene encoding.[96] Snail overexpression enhanced E-cadherin expression while preventing GMF-mediated metastasis suppression. E-cadherin synthesis was determined to be strongly linked to snail prevention. In human breast cancer cells, snail overexpression reduced anti-migration abilities while increasing E-cadherin expression.[97,98] GMF effectively stops mice's lipopolysaccharide-mediated metastases, according to an animal model. For the treatment and prevention of the spread of cancer, GMF may be a novel antineoplastic agent.[99,100]

(x). Salinomycin. Salinomycin is a *Streptomyces albus*-derived monocarboxylic polyether antibiotic.[101] It operates on a variety of biological membranes and has a strong affinity for positive ions, notably potassium, disturbing the equilibrium of ion concentrations between the inside and outside of cells, changing osmotic pressure, and finally causing germ cell disruption.[102] Salinomycin is an anticancer agent to sensitize multidrug-resistant human cancer cells.[101] It particularly destroys cancer stem cells (CSCs), in particular breast cancer stem cells, through a variety of processes like necrosis, autophagy, and apoptosis. Invasion, departure, and proliferation in breast cancer cells have been recognized as being inhibited by salinomycin.[102] It has also been demonstrated to reverse the immune-inhibitory microenvironment, which inhibits tumor growth. Salinomycin is a promising therapy for breast cancer (BC) as a result. Metastasis and recurrence of breast cancer are major causes of mortality due to the breast cancer stem cells (BCSCs) high tumor-initiating potential and resistance to standard cancer treatments.[103] Using salinomycin in conjunction with standard chemotherapy and targeted therapy has been shown to be a highly effective clinical strategy to treat breast cancer, killing both common cancer cells as well as cancer stem cells (CSCs).[21] To a large extent, salinomycin regulates cellular processes in breast cancer cells.[104] A wide range of pathways control cell death and interactions among various biological processes. Activation of mitoptosis, the irreversible breakdown of mitochondrial structure, and the release of other apoptogenic factors from mitochondria are all possible causes of its effects. Recent research indicates that it prevents cancer stem cells (CSCs) in specific cancer types, such as colon cancer, leukemia, as well as breast cancer.[105] The transcription factors β-catenin, c-Myc, Snail, and SOX2 that are linked to cell differentiation in cancer stem cells are inhibited by salinomycin.[106] Salinomycin does not affect normal cells, such as human T lymphocytes, but it causes apoptosis to occur in a variety of human cancer cell types. Salinomycin can also induce apoptosis in cancer cells that have excess Bcl-2, P-glycoprotein, or a 26S proteasome with a higher proteolytic activity, making them resistant to apoptosis and anticancer medications. The tumor suppressor protein p53, caspase activation, the CD95/CD95L system, and the proteasome are not connected to the distinct apoptotic pathway that salinomycin causes. It also is not followed by cell cycle arrest. A549 and HCC4006 are two NSCLC cell lines; salinomycin lowered the variety of nutrient-dense EMT and cell migration when combined with metformin.[107]

(xi). Ciprofloxacin. The second-generation broad-spectrum fluoroquinolones or ciprofloxacin[108] is efficient against *Pseudomonas aeruginosa* and other Gram-positive and Gram-negative bacteria.[23] Ciprofloxacin is easily absorbed when taken by the mouth and is distributed widely. Fluoroquinolones are synthetic antibiotics with a wide range of activity. They work by interacting with topoisomerase II-DNA complexes to stop helix rejoining, which causes double-stranded DNA breaks.[109] Numerous infections, particularly those produced by bacteria in the urinary tract, are treated with it. However, it is thought that the fact that substandard and artificially produced oral ciprofloxacin formulations are available and used in developing countries has increased the risk of bacterial resistance and unsuccessful treatments.[110] Chemotherapy does not work very well for advanced colorectal tumors. Recent research has shown that the quinolone antibiotic ciprofloxacin stops human bladder carcinoma cells from growing and makes them commit suicide (apoptosis).[111] Ciprofloxacin stopped DNA synthesis in all colon carcinoma cells in a way that depended on time and dose, but it did not affect hepatoma cells. Ciprofloxacin stops colon cancer cells from dividing and makes them commit suicide, possibly by stopping mitochondrial DNA synthesis.[112] The growth stop is caused by stopping DNA synthesis, causing mitochondrial damage and then apoptosis. Also, they influenced the immune system by regulating cytokine production, decreasing inflam-

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matory responses, and insulating the liver from the toxic effects of lipopolysaccharide (LPS).[113] In vitro tests on cancer cell lines from humans and animals—a few examples of cancer cell lines are those derived from human bladders, human colons, hamster ovaries, and human livers—have shown that ciprofloxacin kills cancer cells.[114] When p53 is overexpressed, it changes how the cell cycle, DNA synthesis, and cell death are controlled. Anticancer drugs cause cancer cells to die by stimulating the p53 pathway.[115] Various p53-downstream-specific gene products, such as the pro-apoptotic Bax protein, may act on apoptosis. Induction of apoptosis occurs when these products are expressed simultaneously.[116] The Bcl-2 family includes both pro- and antiapoptotic Bcl-2 proteins, which have been shown to cause mitochondrial dysfunction, which is a common early apoptotic activity.[117] P53 can also decrease Bcl-2 expression and initiate oxidative apoptotic marker genes by increasing (ROS) reactive oxygen species levels.[118] Simultaneously, it has been shown, according to a flow cytometric analysis, that human non-small cell lung cancer cells demonstrated a dose-dependent increase in G2/M arrest.[119] Glutathione depletion within the cell demonstrated how ciprofloxacin altered the redox signaling system.[120] Ciprofloxacin resulted in the apoptotic death of MDA-MB-231 annexin V/Propidium iodide staining, which showed the presence of cells. Ciprofloxacin treatment also activated the Bax/Bcl-2-dependent pathway, resulting in a reduction of mitochondrial membrane potential, which in turn promoted apoptosis.[121] The above researchers reported that tumor suppressor activity was enhanced and that oligonucleosomal DNA fragmentation was present. A p53-dependent mechanism may be involved in the regulation of this late-apoptotic process. So, the current study contributes to the understanding of ciprofloxacin's therapeutic potential by giving crucial molecular information showing that the cytotoxicity produced by ciprofloxacin in human triple-negative breast cancer cells may also be explained by a cell membrane cascade.[122]

(xii). Dactinomycin. Dactinomycin is an antineoplastic antibiotic given intravenously that is used to treat solid tumors in children and choriocarcinoma in adult women. There are at least 50 distinct kinds of dactinomycin, commonly known as actinomycin; however, only dactinomycin D and C show any potential for therapeutic use.[116] A polypeptide antibiotic called dactinomycin D is produced from the Str. Parvulus nourishing solution.[123] Chemotherapy is still the best way to treat the majority of cancers. Some cancer chemotherapies can cause premortem stress signals that contribute to immunogenic cell death (ICD),[124] which triggers an immune response against cancer and slows the growth of tumors over time. Dactinomycin D is a strong inducer of immunogenic cell death (ICD) that has anticancer effects in living organisms that depend on the immune response.[125] A common DNA-to-RNA transcription inhibitor is dactinomycin D. Transcription and secondary translation were both reduced by a group of pharmacological immunogenic cell death (ICD) stimulators.[126] Inside the molecules, a phenoxy ring structure links two allelic cyclic chains of peptide.[127,128] It has been demonstrated how this peptide chain can interact with DNA's deoxyguanine, dactinomycin D binding to the DNA double helix, and begin creating a structure through the nucleus that prevents RNA polymerase from performing its function, RNA synthesis, and mRNA synthesis, and thus the occurrence and development of cancer.[129]

(xiii). Azithromycin. A macrolide antibiotic called azithromycin is used to treat bacterial infections.[59] Macrolide antibiotics worked well either on their own or with other treatments.[130] Additionally, by inhibiting the terminal stage of autophagy, macrolide antibiotics can work against tumors in other ways, such as by causing apoptosis,[130] by inhibiting cancer angiogenesis, or by treating as an anticarcinogenic agent. Azithromycin has been shown to work against cancer in addition to fighting off infections.[131,59] Azithromycin binds to the bacterial 50S ribosomal subunit. Besides preventing the transpeptidation/translocation process as well as the synthesis of the 50S ribosomal subunit, it prevents the production of proteins.[132] Recent studies have identified azithromycin as a potential approach to stopping the proliferation of HeLa and SGC-7901 cancerous cells by causing them to undergo a process known as apoptosis.[133] Azithromycin (AZM) promotes autophagy. Furthermore, it has been observed that antibiotics may influence tumor formation by targeting mitochondria and destroying cancer stem cells.[134] Autophagy inhibitory effects are enhanced by tyrosine kinase inhibitors or proteasome inhibitors are used as adjuvant treatments[135] to investigate the effect of AZM and DNA-damaging agents in non-small-cell lung cancer (NSCLC) cells. It is used in combination with doxorubicin (DOX), Etoposide, as well as carboplatin NSCLC cell lines. These DNA-damaging drugs became more deadly to cells when combined with AZM, but AZM alone had virtually no cytotoxicity, according to research by Toriyama et al. (2021). Because ATG5-KO and TP53-KO cells reduced AZM-enhanced cytotoxicity, it became clear that this improved p53 wild-type and the potential to induce apoptosis were to form autophagosomes.[136] AZM was reported to decrease autophagy, which led to a rise in lysosomes and autolysosomes.[129] Therefore, its DOX and AZM combination led to an elevated level in lysosomes, which were able to break down autolysosomes, causing a significant amount of lysosomal membrane permeabilization (LMP) to induce apoptosis. Combined treatment with AZM and DNA-damaging drugs, according to Toriyama et al. (2021), is an effective method for NSCLC treatment because of high LMP induction.[136,137]

(xiv). Clarithromycin. A well-known macrolide antibiotic called clarithromycin (CAM) is offered as a generic drug. Clarithromycin has been used for a long time to treat bacterial infections, Lyme disease, and gastric infections caused by *Helicobacter pylori*. A lot of preclinical and clinical data show that complementary and alternative medicine clarithromycin might be able to help treat some types of tumors in addition to conventional treatment.[138] It works against tumors in several different ways. Pro-inflammatory cytokine levels are reduced over time, autophagy is inhibited, and angiogenesis is suppressed. Many cancers, including multiple myeloma, lymphoma, chronic myeloid leukemia (CML), and lung cancer, are among the cancers against which it is most effective. Researchers Petroni et al. (2020) are studying how the macrolide antibiotic clarithromycin controls autophagy in cancer cells to keep them alive and resistant to chemotherapy. Petroni et al. (2020) demonstrated that clarithromycin inhibited the development of human colorectal cancer cell (CRC) lines by regulating autophagic flux and inducing apoptosis. Autophagy depletion is indicated by an increase in cytosolic autophagosomes as well as changes in the LC3-II and p62/SQSTM1 autophagy markers.[139] Petroni et al. (2020) examined if the effects of clarithromycin depended on hERG1 and its morphological changes because the drug is known to

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bind hERG1 K^+ channels. Using hERG1 mutants with different gating characteristics, Petroni et al. (2020) demonstrated that the fluorescence microscopy of clarithromycin interacts with stopped channels selectively. Clarithromycin also stopped the PI3K p85 subunit and hERG1 from forming a macromolecular complex by locking the channel in a resting position.[140] Due to this, Akt phosphorylation was considerably decreased and p53-dependent cell death was triggered, as seen by activating late caspases. Subsequently, clarithromycin elevated the harmful effects of 5-fluorouracil (5-FU), the primary chemotherapeutic drug for CRC.[141] In vitro, in vivo, and human models conclude that clarithromycin alters autophagic flow by interfering with the signaling pathway that connects hERG1 and PI3K.[142] Clarithromycin in combination with 5-FU could be a unique treatment option for CRC.

(xv). Erythromycin. The antibiotic erythromycin belongs to the macrolide class. Various respiratory diseases, such as community-acquired pneumonia and Legionnaires disease, have generally been treated with it.[139] Erythromycin seems to be beneficial toward both Gram-positive as well as Gram-negative bacteria, in addition to a variety of other microorganisms. It does this by stopping proteins from being made and interacting with the structure of 23S rRNA, which can be determined in the 50S subunit of bacterial ribosomes. It stops the small molecule chain early, departing the cell. Human tissues only contain the 40S and 60S subunits; consequently, erythromycin does not affect the production of proteins there, not the 50S subunits.[143] It has been shown to kill tumor cells by blocking hERG1 and shutting it down. In this study,[144] erythromycin-treated neuroblastoma cells (SH-SY5Y) were researched in a range of timings and doses. The MTT assay was used to measure cell viability and cell proliferation, respectively. The variability of cell cycle phases and the concentration of calcium in the cytosol were assessed by using flow cytometry. Using fluorescence microscopy and JC-1 probe labeling, the mitochondrial membrane potential was determined. C-Myc, an oncogene, p21 (WAF1/Cip1), and a tumor suppressor protein expression analysis were done by Western blotting.[145] According to time and concentration, erythromycin may slow the growth of SH-SY5Y cells. The cell cycle is complete when it reaches the S phase. In SH-SY5Y cells, erythromycin treatment results in mitochondrial membrane potential breakdown and an excess of calcium in the cytoplasm.[146] Down-regulation of the c-Myc protein was accompanied by an up-regulation of the p21 (WAF1/Cip1) protein. Erythromycin may prevent the proliferation of SH-SY5Y cells.[147] Erythromycin being able to kill cancer can indeed reduce the transcription of the proteins, c-Myc and p21 (WAF1/Cip1).[148]

OPPORTUNITIES AND OBSTACLES OF CANCER TREATMENT WITH ANTIBIOTICS

When compared to standard cancer treatments such as radiation, targeted therapy, surgery, chemotherapy, and immunotherapy, the crucial advantage of antibiotics is that they enhance survival and reduce side effects. In the treatment process for cancer, surgery can only cure the local malignancy; it cannot completely remove the cancer cells that have spread to the bloodstream. For this reason, to eliminate the cancer and lower the chance of recurrence, systemic medication therapy with antibiotics may frequently be used after cancer surgery. To provide a therapeutic effect, chemotherapy radiation lowers the quantity of cancer cells. However, most cancer patients will experience a relapse after receiving radiotherapy, which is also a challenging issue in the field of cancer biology today. The growth of cancer stem cells (CSCs) is the main cause of this.[149] Thus, removing cancer involves first eradicating the CSCs. Numerous studies have demonstrated that anticancer antibiotics can effectively decrease the risk of cancer recurrence by damaging cancer stem cells in a novel manner through rapid detection. Usually, cancer cells develop more quickly than the healthy cells from which they developed.[150] Acute leukemia and choriocarcinoma are two examples of rapidly proliferating cancers that respond to antitumor drugs and can also be cured with chemotherapy.[150] A new class of chemotherapeutic agents is antibiotics that targets cancer. Current research suggests that the anticancer antibiotic was found through the Cancer Chemotherapy National Service Center (CCNSC), which can kill cells at all stages of the cell division cycle, including G0 cells, and reduce the ability of cancer cells to evade cancer antibiotics. This is supposed to make it easier to stop cancer cells from growing.[151] Immunization is a common way to treat cancer, and it works for about three months, so it is best to start as soon as possible. Combination therapy antibiotics can now enhance the body's immune system, invade cancer, enhance the overall situation, speed up the healing process, and prevent cancer from coming back or spreading.[152]

The drawbacks of using antibiotics to treat cancer include the potential development of antibiotic resistance. This occurs when bacteria adapt and become resistant to the antibiotics being used, making infections more difficult to treat.[21] Antibiotic resistance can lead to prolonged or recurrent infections, compromising the effectiveness of cancer therapy and posing significant challenges for patient management.[153] Additionally, antibiotic-resistant infections may require alternative, more potent antibiotics, increasing the risk of side effects and contributing to healthcare costs. Antibiotics can inhibit the immune response and promote inflammation, which may impact cancer treatment, especially when taken during chemotherapy.[154,155] This can lead to lethal bloodstream infections (BSIs) and other complications. This can affect the outcome of immunotherapy and reduce its effectiveness. Studies have suggested that past use of antibiotics may be associated with a higher risk of developing cancer. Therefore, antibiotic stewardship and careful management of antibiotic use are essential in cancer treatment to minimize the risk of antibiotic resistance and optimize patient outcomes. Although reducing drug resistance in cancer is a significant challenge, researchers are exploring several strategies to address this issue. Some approaches, such as combination therapies that target numerous pathways implicated in drug resistance and personalized therapy techniques that rely on the genetic profile of individual tumors, are utilized in the context of cancer treatment to address the issue of drug resistance. Moreover, researchers are always looking for new therapeutic targets and approaches to enhance the efficacy of anticancer drugs and prevent drug resistance in cancer cells.

ON-GOING RESEARCH/MAJOR FINDINGS OF ANTICANCER ANTIBIOTICS

Lactoquinomycin, which is related to mitomycin but distinguished from it through its physicochemical features and capacity to remove cancer, was recently discovered as a result of research on enediyne antibiotics. It appears that lactoquinomycin is more stable and has strong anticancer

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action.[156] Natural product N1999A2, which is based on a nine-membered enediyne, exerts anticancer effects on human cancer cells. With DNA intercalation into the minor groove, it was discovered to be remarkably stable and contains chromospheres that resemble those of neocarzinostatin. The presence or lack of an aminoglycoside residue accounts for the only difference in the two drugs' modes of action.[157] For several of these antibiotics, improved drug delivery methods have also led to a rapid release of the medicine, such as with one aqueous or two polar block-containing flower-like microspheres that are anticancer pH-sensitive. When the pH was altered to highly acidic, as in tumor extracellular pH, the hydrophobic nature of the flower-like micelles altered, causing the microsphere core to rupture and enabling rapid release of drugs.[158] For doxorubicin, we also created adjacent fluorescent probes on reduction-sensitive polymeric nanocarriers. They demonstrated elevated release characteristics when glutathione was present. Research findings show that they can enter cells through endocytosis, as proven by cellular uptake, and that this process improves porosity and preservation.[159] Researchers have found that doxorubicin nanoparticles have a massive dose and that their therapeutic effects get better over time.[160] Both finding novel antibiotics and rediscovering already-known antibiotics have been the subjects of extensive research in recent years. It is well-known that distamycin targets the DNA's minor groove in particular. Lexitropins, which include a thiazole component and are closely linked to distamycin, have also demonstrated comparable mechanisms of action.[161] *Streptomyces griseous* is fermented to produce the anthraquinone antibiotic chromomycin A3. It can prevent the synthesis of large molecules by interacting reversibly and completely using the DNA template when divalent metal ions such as Mg^{2+} are present. New studies have found that chromomycin A3 and Mg^{2+} form two different types of compounds with distinct stoichiometries and formation variables. These complexes bind to DNA in various ways.[162] Mithramycin, also known as plicamycin, is a drug that has been taken off the market. It was an antitumor antibiotic that bound to DNA, also first found in *Streptomyces griseous*. It was used as a chemotherapeutic agent and worked by stopping replication and transcription. Thus, it prohibited the formation of macromolecules when a bivalent cation such as Mg^{2+} was present due to its reversible interaction with DNA.

FUTURE PERSPECTIVES AND CONCLUSIONS

Antibiotic discovery and application in common clinical settings have unquestionably been some of the most significant medical advances of our time. Their use resulted in a significant reduction in infectious-disease-related death rates and helped contribute to a worldwide increase in human life expectancy. According to the endosymbiotic hypothesis, prokaryotes and eukaryotes are thought to have an evolutionary relationship. Since there is growing evidence that a variety of antibiotics can damage mammalian mitochondria, many researchers in medical and scientific fields nowadays promote the use of antibiotics for conditions other than microbial infections. Scientists have discovered that they also inhibit the growth of eukaryotic cells, which may be related to their common evolutionary link with prokaryotes. Drug repurposing of selected antibiotics is an emerging approach to cancer drug discovery. This strategy involves identifying and utilizing existing drugs, such as antibiotics, for new therapeutic purposes in cancer treatment. Although repurposed drugs have already been approved for other indications, their development time can be greatly shortened, resulting in lower costs, as the regulatory process for repurposed drugs is shorter than that for new drugs. With the potential for novel modes of action, repurposed drugs can open up new routes that were not previously investigated in their original indications, perhaps leading to more effective cancer treatments. Antibiotics can improve the diagnosis and lessen the adverse consequences of cancer treatment when compared with standard treatments such as surgery, radiation, chemotherapy, immunotherapy, and targeted therapy. However, there are some adverse effects to consider, such as the disturbance of the gut microbiota, which can lead to an increased risk of infections and lower efficiency of certain cancer treatments. Excessive use of antibiotics can increase the risk of antibiotic resistance and contribute to the formation of antibiotic-resistant bacteria, which can make it more difficult to treat infections in cancer patients. In conclusion, the drug repurposing of selected antibiotics is a promising approach to cancer drug discovery. Further research is needed to optimize the use of antibiotics in cancer therapy and minimize their negative effects.

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All authors participated sufficiently in the work to take public responsibility for appropriate portions of the content. S.S.M.: Collection of content and supervision of the research group, conceptualization, supervision, writing and editing, designed and oversaw the study. N.B.: Drafting the manuscript.

Notes

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