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Review Article

Efflux Pumps, Biofilms, and Tumor Resistance: Converging Mechanisms in Microbial and Cancer Survival: A Narrative Review

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Abstract

Drug resistance is one of the greatest obstacles to pharmaceutical success in contemporary medicine and has greatly restricted both antimicrobial and therapeutic approaches to cancer. While microbial multidrug resistance and cancer chemoresistance have been traditionally considered discrete processes, there is growing evidence that they have a number of common survival mechanisms. This narrative analysis critiques and clarifies drug-resistant bacterial pathogens and cancer cell molecular, structural, and physiological processes, including efflux pumps, biofilm-associated protection, and tumour microenvironment-mediated resistance. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar for papers on multidrug resistance mechanisms in microbial and cancer systems. This review shows how bacterial resistance-nodulation-division (RND) and cancer-associated ATP-binding cassette (ABC) transporters reduce intracellular drug accumulation and favour treatment failure. Biofilms and solid tumours have remarkable parallels in their extracellular polymeric matrices, which hinder medication penetration and let resistant cell populations survive. Emerging efflux pump inhibitors, antimicrobial peptides, drug delivery systems based on nanocarriers coupled to microenvironmental surveillance and microenvironment targeting technologies are considered among promising mechanisms for combating multidrug resistance. With much advancement, clinical translation continues to be constrained by toxicity, low selectivity, and resistance network complexity. In general, we emphasize that microbial and cancer resistance have in common the adaptive strategies and underscore the critical need for multi-domain strategies to develop optimized therapies against multidrug resistance.

Keywords
Antimicrobial resistance, Biofilm, Cancer chemoresistance, Efflux Pumps, Tumour.

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Introduction

Chemotherapy resistance is one of the biggest clinical difficulties. Pharmacologists and doctors have struggled to overcome drug resistance in malaria, HIV/AIDS, bacterial infections, and cancer. Medication resistance results from inappropriate medication use, antimicrobial misuse, and poor drug quality. Drug resistance causes greater mortality and morbidity, higher medical costs, diagnostic ambiguities, and distrust in traditional medicine. Thus, more effective and tolerant antimicrobials must be found. This review explains efflux pump processes and chemical architectures, which aid antimicrobial drug creation [1].

Paul Ehrlich developed chemotherapy and the Magic Bullet, a germ-killing technique that left patients unharmed. He later developed a Treponema pallidum-induced syphilis treatment, the only option for 20 years [2]. Medical research changed once Sir Alexander Fleming discovered penicillin from Penicillium notatum. This discovery helped millions of WWII soldiers fight the "invisible enemy" with medication. Many antibiotic-related events have occurred in medicine, and WHO lists drug resistance as one of the top three public health challenges of the 21st century [3].

Bacterial antibiotic resistance threatens clinical science, and due to their shorter lifespans, bacteria are more susceptible to genetic variation and evolution than eukaryotes. MRSA, Mycobacterium tuberculosis, Pseudomonas aeruginosa, Acinetobacter, and other gram-negative bacteria share resistance [4]. Drug-resistant plasmids (R) or transposons that encode drug-resistant genes, efflux pumps, or both produce multidrug resistance in bacteria. Target-protein changes can render bacteria drug-resistant. The erm gene methylates adenine at 50s rRNA location 2058, generating drug-resistant bacteria. Drug resistance results from phosphorylation, adenylation, acetylation, and hydrolysis of natural antibiotics. Horizontal gene transfer between bacteria is an intriguing antibiotic resistance mechanism. Horizontal gene transfer (HGT) employs plasmids or transposons to transfer genetic material to a non-descendant cell [5].

Cancer treatment often involves chemotherapy, and clinical oncologists say patients develop cancer resistance to new drugs. This decreases chemotherapy effectiveness. In several studies, cells in vitro are exposed to chemotherapeutic drugs and develop drug resistance. Parent cancer cells pass on multidrug resistance to daughter cells. Mutations in MDR proteins, notably ABC transporters, cause drug resistance. Normal physiological processes, including signal transmission, extracellular material absorption, cellular transport and excretion, protein or hormone synthesis, lipid transport, and xenobiotic avoidance, are affected. MDR's in vivo mechanism is unknown. Despite continuing research on alternative transporters, P-glycoprotein (P-gp/ABCB1) is the main source of MDR in malignancies. The kinetics of P-gp enable it to recognize many substrates. Many ABC superfamily transporters are reviewed here [6].

Despite extensive research on bacterial efflux pumps and tumor drug resistance, few integrative studies analyze their structural and biochemical convergence. Most research focuses on antimicrobial resistance or oncologic MDR, but few studies address survival mechanisms. such as ATP-driven drug extrusion, metabolic adaptation, and extracellular barrier formation. Additionally, dual-purpose efflux pump inhibitors' translational potential remains untested. To identify cross-targeting treatments, this article compares biofilm-associated resistance and tumor microenvironment-mediated chemoresistance at the molecular level.

Literature Search Strategy

A systematic literature search was undertaken in January and February 2026 to find research on microbial pathogen and cancer cell multidrug resistance pathways and particular emphasis on high-quality publications published during last five years. The main scientific databases PubMed, Scopus, Web of Science, and Google Scholar were searched.

The search strategy included keywords and Boolean operators, such as efflux pumps, ABC transporters, RND transporters, multidrug resistance, drug resistance, biofilm, biofilm-associated resistance, tumor microenvironment, cancer chemoresistance, and tumor. Other keywords, including antimicrobial resistance, microbial survival mechanisms, cancer survival pathways, efflux pump inhibitors, and multidrug-resistant organisms were searched.

The review focused on papers published between January 2015 and February 2026, especially in the recent five years. English-language original research articles, review articles, systematic reviews, and high-impact research papers on microbial drug resistance, cancer chemoresistance, efflux transport systems, biofilm-mediated protection, tumour microenvironment-associated resistance, or therapeutic strategies targeting these mechanisms were added, other to resistance mechanisms, lacking scientific significance, duplicate papers, conference abstracts without full-text access, non-English publications, or research on other biological processes were removed.

Initial database searches yielded 185 results; with title and abstract screening, 112 articles were screened after deleting duplicates and irrelevant ones. After full-text evaluation, 73 papers were included in this narrative review. Key article reference lists were manually screened for additional relevant references. Literature spanning microbiology, infectious illness, oncology, molecular biology, and pharmacology was independently assessed and compared to cover both microbial and cancer resistance pathways. The research was then categorized by primary themes: efflux pumps, biofilms, tumor microenvironments, multidrug resistance mechanisms, and new therapeutic strategies.

Efflux pump anatomy, function, and drug resistance

Efflux-Pumps

All living cells include efflux pumps to prevent organic chemical toxicity. Physical properties, not chemical compositions,

let pumps recognize many compounds as substrates. General efflux pump systems have two types, Prokaryotic efflux pumps protect viruses and bacteria [7]. Protozoa, fungi, and cancer cells exhibit drug-resistant eukaryotic efflux pumps. Pumps mediate prokaryotic and eukaryotic cell resistance, making the division imperfect [8].

Health Benefits of Efflux Pumps

Under normal conditions, the kidney, liver, and epithelial tissues that protect the small intestine, placenta, blood brain barrier, and testes produce efflux pumps. Efflux pumps restrict the absorption of some drugs in the small intestine, and safe against drugs and toxins, brain. An efflux pump removes harmful substances from brain cells and changes blood-brain barrier endothelial cells. Wang and colleagues reported that P-glycoprotein-deficient mice exhibited higher brain vincristine levels. Active placental efflux pumps maintain pharmacological barriers. The maternal surface of placental microvilli's syncytial membrane has primarily ABC pumps [9].

Sertoli cell membranes form the blood-testis barrier (BTB) to protect spermatozoa from harmful chemicals and drugs and prevent antibodies from developing against sperm cells during spermatogenesis. Sertoli cell membrane efflux pumps remove harmful substances [10].

MRP2 and P-glycoprotein release conjugated bilirubin from hepatocytes into bile canaliculi; Dubin-Johnson syndrome reduces bilirubin excretion owing to MRP2 deficiency. P-glycoprotein secretes cholesterol and uric acid to protect proximal tubular epithelial cells. By blocking renal epithelial cell P-glycoprotein from secreting digoxin, ceftazidime, and other drugs, verapamil, reserpine, vinblastin, and daunorubicin reduce tubular digoxin secretion [11].

Efflux Pump Form and Function

Basic efflux pumps let bacteria adapt to environmental challenges via osmotic control and evacuation of harmful chemicals, including bile salts and toxins, as well as pathogenicity, biofilm formation, and interbacterial communication. Gram-negative bacteria need efflux pumps for drug resistance. The structure and energy source of bacterial efflux systems split them into major categories. ABC superfamily substrate extrusion uses ATP hydrolysis. Protons or sodium ions power resistance-nodulation-division (RND), major facilitator superfamily (MFS), small multidrug resistance (SMR), multidrug and toxic compound extrusion (MATE), proteobacterial antimicrobial compound efflux (PACE), and p-aminobenzoylglutamate transporter (AbgT) families [12], Table 1.

The ABC, MFS, and RND families are the only Gram-negative bacteria with tripartite efflux systems that penetrate both membranes and are connected to antibiotic resistance. This article discusses these three families due to their structure and clinical value. An exit duct-forming OM channel, a substrate-recognizing IM transporter, and a PAP are typical complexes. Structural data is available for the RND pumps AcrABZ-TolC, AcrD and OqxB components (which combine with membrane fusion proteins AcrA and OqxA and the outer membrane channel TolC), EmrAB-TolC, and MacAB-TolC. Structures using cryo-electron microscopy and X-ray crystallography highlight EPI efflux processes and rational design [13].

Table 1. Comparison of major efflux pump families associated with drug resistance.

Feature	RND Efflux Pumps (Bacteria)	ABC Transporters (Cancer Cells)
Representative proteins	AcrAB-TolC, MexAB-OprM	ABCB1 (P-gp), ABCG2, ABCC1
Main organisms	Gram-negative bacteria	Human cancer cells
Energy source	Proton motive force (PMF)	ATP hydrolysis
Function	Antibiotic extrusion	Chemotherapeutic drug extrusion
Clinical significance	Antimicrobial resistance	Multidrug resistance (MDR)

Efflux pump mechanisms

Drug ejection from efflux pumps generates MDR, one of several antibiotic resistance pathways. Overexpression of efflux and drug transporters reduces intracellular drug accumulation and causes clinically relevant drug resistance. This causes most tetracycline, erythromycin, and fluoroquinolone resistance. It is also the main chemotherapeutic resistance mechanism. Though numerous classes affect resistance in prokaryotic and eukaryotic species, efflux pump mechanisms are different. Six bacterial efflux pump classes and five eukaryotic pump groups exist. The majority of multidrug resistance is caused by ABC efflux pumps [15]. The 48 human ABC transporter genes have seven subfamilies from ABCA to ABCG. Known multi-drug-resistant proteins include P-glycoprotein. The human ABCB (MDR/TAP) family includes ABCB1. ABC transporters contain four domains: two NBDs bind and hydrolyze ATP, and two TMDs detect and transport substrates. The kidney, liver, and epithelial tissues express ABC transporters to transport hormones, lipids, ions, xenobiotics, and other compounds across cell membranes, and some of 48 ABC transporters bind numerous substrates. Some carry anticancer or antibacterial drugs, causing medication resistance, and ABC transporters pump substrates against chemical gradients via ATP hydrolysis. ABC transporters act in one way physiologically, even if drug efflux pumps are reversible. ABC transporters use a switch, an alternating site, and continuous contact. ATP-dependent NBD dimerization and substrate binding to the TMD and its switching between outward- and inward-facing conformations are common to all these theories. Understanding drug transporter mechanisms

and efflux pump inhibitor development is essential for anti-drug resistance strategies [16].
Despite substantial efflux transporter characterization, numerous issues persist, so efflux pumps' role in complicated tumor systems is still contested compared to metabolic adaptability and target mutation. In addition, ABC transporters, including ABCB1 are involved in multidrug resistance, although therapeutic inhibition techniques have failed, raising issues regarding whether exporter activity drives or marks resistance.

EPI target potential

The literature describes efflux pump resistance-reducing drugs using several terms. Though sometimes used interchangeably, these terms refer to distinct systems or acts. This review covers direct blocking, functional disruption, and competition as EPI and adjuvant. Multiple methods block efflux pumps from releasing antibiotics, and several EPI mechanisms have been revealed or anticipated [17, 18].
Several mechanisms have been suggested for the inhibition of efflux pump activity. Efflux pump inhibitors (EPIs) have been reported to work on basic efflux structures, such as AcrA, AcrB, and TolC, or also on the downstream regulatory pathways that activate them. Moreover, some EPIs interfere with the establishment of working efflux complexes in the bacterial membrane, which leads to decreased transporter function. Others are energy-limiting agents that decrease the energy required during active transport via dissipation of the proton motive force (PMF) [19], and some inhibitors in such compounds physically obstruct substrate-binding pockets or transport channels, including the deep binding pocket (DBP) of AcrB and the TolC channel. In addition, EPIs might disrupt allosteric conformational transitions necessary for substrate extrusion, compete with antimicrobial agents for substrate-binding sites, or saturate transporter systems through excessive substrate occupancy. All these mechanisms reduce drug efflux and increase intracellular antibiotic accumulation, thereby enhancing antimicrobial efficacy [20].
EPI must bind more strongly than the natural substrate for competitive inhibition. The efflux cycle cannot be completed by transporter protomers altering conformation due to this binding. The steric barrier created by EPIs impairs the transport cycle conformational cascade. EPIs substrate-dependent. For instance, PAβN (phenyl-arginine-β-naphthylamide) competes with RND pump DBP substrates and disturbs AcrB's dynamic conformational cycling. Both PAβN and ciprofloxacin bind DBP; they interact with different residues, limiting direct competition. In contrast, PAβN binds DBP to decrease AcrB conformational changes. Most EPIs in development directly bind to efflux proteins, while some have unclear mechanisms. Few medications target gene expression or allosteric regulatory areas [21].
Efflux pump inhibitors' therapeutic use remains uncertain after years of study, due to toxicity, poor selectivity, and drug kinetic constraints. Several first- and second-generation inhibitors failed, and it is unclear whether inhibition of efflux pumps alone is sufficient to overcome resistance, or whether it is combined with modulation of metabolic and apoptotic pathways.

Genetic Regulation of ABC Transporters in Cancer

Cancer resistance to numerous medications depends on the genetic regulation of ATP-binding cassette (ABC) transporters, notably ABCB1 (P-glycoprotein), ABCC1 (MRP1), and ABCG2 (BCRP). These cells actively restrict drug accumulation and reduce treatment efficacy. Due of complex regulatory networks such chromosomal variation, translational regulation, and epigenetic alteration, tumours express them variably [22].
The ABC transporter gene's effects on patient drug responsiveness and ABCB SNPs like C3435T, ABCC1, and ABCG2 impact transporter expression, protein stability, and substrate selectivity are mysteries. Some studies indicate strong connections with treatment outcomes, while others have minimal predictive significance. This range suggests that polymorphisms alone are poor predictors and need biological context [23]. Pharmacogenomic ABC transporter profiling predicts drug distribution, toxicity, and therapeutic response. Transporter genotypes and drug-specific characteristics increase dose and treatment selection. Lack of clinical standards, tumour heterogeneity, and dynamic gene expression changes following treatment hamper pharmacogenomic deployment. Many studies employ peripheral or germline genetic data, which does not reflect tumor-specific transporter regulation [22].

Recent Advances in Efflux Transporter

Current efflux transporter research has advanced from descriptive characterisation to mechanism-driven and accurate therapeutics. Advanced cryo-electron microscopy (cryo-EM) has enabled high-resolution structural explanations of ABCB1 and ABCG2 transporters. Because these studies reveal conformational states, substrate-binding cavities, and ATP-driven transport cycles, they provide a structural basis for rational drug planning. Instead of empirical screening, structural insights are being used to identify allosteric and substrate-type inhibition sites [24].
ABC transporter inhibitors have made progress alongside clinical trials. Initial efflux inhibitors like verapamil and tariquidar suppressed efflux activity, but toxicity and pharmacokinetic interference restricted their clinical usage. Selective modulators like repurposed kinase inhibitors, natural bioactive chemicals, and next-generation small molecules limit transporter activity while preserving physiological functions. Combining efflux inhibition with chemotherapy to improve intracellular drug retention and therapeutic effectiveness is a current development [25].
The different epigenetic and chromosomal control are also of central importance in elucidating transporter-mediated resistance. The production of ABCB1, ABCC1, and ABCG2 is regulated by gene amplification, promoter methylation, and

non-coding RNAs, including microRNAs and long non-coding RNAs. Therefore, efflux-targeting strategies with drug discovery and tailored oncology are becoming popular, and in order to reveal patient-specific resistance mechanisms and optimize targeted therapies, future treatment protocols are expected to utilize structural biology, genetic profiling, and microenvironmental investigation [26].

Biofilm Formation and Microbial Protection

Methods of Biofilm Development

The biofilm formation is a multistage, closely controlled process. Free-floating bacteria attach to surfaces by weak physicochemical forces such as van der Waals and electrostatic attraction. Flagella and type IV pili are integral for surface sensing and transient adhesion during this time, and adhesion and EPS production rise, as cells are anchored to the substrate [27].

The biofilm grows with microcolony and architectural differentiation. Planktonic microorganisms are attracted to multiplying cells and produce a complex extracellular matrix. Quorum sensing systems activate stress adaptation, nutrition acquisition, and community shaping gene expression programs when cell density rises. In mature biofilms, three-dimensional heterogeneity permits water routes to transport nutrients and eliminate waste. Structures are complicated due to metabolic stratification, where oxygen and nutrient gradients form physiologically distinct subpopulations. Dispersion ends biofilm growth. Environmental stress, dietary restriction, and signaling release biofilm matrix cells. These distributed cells colonize elsewhere because they vary from planktonic and sessile cells. Biofilm life cycles include attachment, community structure, and dispersion to survive [28].

Biofilms are known to cause antimicrobial resistance, but their involvement in persistent genetic resistance is unclear, and several investigations suggest biofilm-linked resistance is phenotypic and reversible, while some claim it increases mutation and horizontal gene transfer. The relative importance of efflux pumps and matrix-mediated diffusion barriers in resistance systems is also unclear. An additional issue is whether biofilm structure alone or metabolic and genetic changes are needed to restore antibiotic resistance.

Extracellular Polymatrix

Extracellular polymeric matrix forms and functions biofilm. Polysaccharides, proteins, eDNA, and lipids comprise the dynamic, chemically complex matrix. Its composition is variable according to species and environments but provides mechanical stability, spatial order, and protection. Polysaccharides form the bulk of the matrix and provide viscoelasticity to shield the structures against shear forces. Proteins such as enzymes and structural adhesins enhance the community cohesion and metabolic flexibility. Extracellular DNA is generated during autolysis or active secretion and stores horizontal genes [29].

The matrix creates microclimate, and controls diffusion, oxygen, nutrition, and chemical gradients. Differential gradients enable cells to slow down or become dormant. The matrix binds and sequesters antimicrobials, reducing their efficiency before bacteria reach them. For instance, electrostatic interactions between matrix components and positively charged antibiotics delay penetration and improve tolerance. Importantly, the matrix aids cell communication. Quorum sensing molecules improve signal strength and coordinate gene expression in their limited design. The extracellular polymeric matrix regulates, not simply protects. Biofilm microbial physiology is characterized by structural cohesiveness, chemical defense, and collective flexibility [30].

Biofilm drug tolerance

Biofilm drug tolerance is a major clinical issue in chronic and device-related infections, and mediated tolerance is phenotypic and reversible, unlike chronic mutations or acquired resistance genes. It significantly affects antibacterial efficacy. Mature biofilm cells can resist antibiotics several orders of magnitude better than planktonic cells. Tolerance has several reasons. Insufficient antibiotic penetration through the extracellular matrix delay or reduce drug exposure, especially for big or positively charged compounds [31]. Reduced metabolic activity reduces antibiotic susceptibility because many antibiotics affect active biological processes involving cell wall building or protein translation. Rare, exceptionally tolerant persister cells may survive deadly antibiotic exposure without resistance mutations, making therapy challenging. Efflux pumps and stress-response pathways stimulated by biofilm formation boost adaptive defenses. Under antimicrobial pressure, oxidative stress, toxin–antitoxin modules, and tight response signaling extend life. Infection requires surgery or treatment despite therapy. Biofilm-mediated tolerance boosts genetic resistance. Repeated sublethal biofilm exposure causes horizontal gene transfer and mutation. Biofilm-associated tolerance relates phenotypic persistence and evolutionary adaptive resistance [32].

Biofilms and solid tumors may have differences, but their structural and functional similarities lead to treatment resistance. Bacterial biofilms possess a thick protective barrier comprised of polysaccharides, proteins, lipids, and extracellular DNA, while solid tumors possess a complex extracellular matrix of collagen, fibronectin, and hyaluronic acid. Although each matrix can have a different composition, both matrices impede drug diffusion and diminish concentrations of the therapeutic agent at target sites. They also develop different microenvironments with nutritional gradients, oxygen deprivation, and altered cellular metabolism that allow specialized resistant cell populations to flourish. Biofilms and tumor tissues may rely upon extracellular barriers, metabolic adaptability, and reduced drug penetration to survive and cause treatment failure and multidrug resistance.

Tumor Microenvironment and Solid Tumor Barriers

Hypoxia and Reprogramming: Tumour development out-

paces blood vessel supply, causing a cycle of hypoxia and cycling. Low oxygen tension stabilises HIF-1α and HIF-2α, which regulate adaptive survival pathways via transcriptional control. HIF signalling causes cancer cells to switch to glycolytic metabolism with oxygen, the Warburg effect. Hypoxia-induced metabolic reprogramming increases biosynthetic capacity, apoptotic resistance, and reactive oxygen species-dependent therapy resistance. High lactate acidifies the environment, reducing immune cell function and encouraging invasiveness. Hypoxia increases physiologic stress and molecular flexibility, improving tumour survival and therapeutic resistance [33].

Cancer cells, cancer-associated fibroblasts, and infiltrating immune cells alter solid tumor ECM. Collagen, fibronectin, and hyaluronan overgrowth stiffens tissue, whereas matrix metalloproteinases and other proteolytic enzymes destroy structural components. This new design profoundly impacts tumor behavior. Matrix density activates mechanotransduction signaling pathways, including integrin-mediated focal adhesion kinase, promoting proliferation and migration. ECM remodeling helps local invasion by creating stromal tissue routes of least resistance, and changed ECM affects medicine distribution, immune cell infiltration, and tumor development. Thus, tumor matrix biochemical and mechanical properties cause illness, not passive structural changes [34].

As a kind of extracellular matrix, extracellular DNA (eDNA) electrostatically binds positively charged antimicrobial drugs. In addition, Pseudomonas aeruginosa biofilms store cationic drugs in negatively charged polysaccharides, such as alginate and Pel, decreasing drug penetration and antibacterial effectiveness. These interactions make biofilm more tolerant and hinder antibiotic therapy [34].

Physical Drug Blockers: Solid tumors provide significant physical medicine delivery challenges. Chemotherapeutic drugs are unevenly distributed by poorly structured vasculature. Higher interstitial fluid pressure from leaky arteries and poor lymphatic drainage limit convective diffusion into deeper tumors. Dense extracellular matrix increases monoclonal antibody and big compound diffusion. Hypoxic core cells remain subtherapeutically exposed while peripheral tumor cells receive cytotoxic doses. Microdomains that cause post-treatment relapse are preserved by geography. Physical resistance is independent of genetics, treatment must address delivery restrictions and biological targets [35].

Cellular Chemotherapy Drug Resistance

MDR Cell Line Culture

Cultured cell lines exposed to increasing dosages of cytotoxic or chemotherapeutic drugs in vitro develop resistance via several pathways, as known for over 30 years. Cytochrome P450 degradation, sequestration, enhanced DNA repair, insensitivity to drug-induced apoptosis, and interaction with drug entry and accumulation, including active removal from cells, create drug resistance, and antimicrobial stress makes microorganisms resistant [36].

The stepwise selection with colchicine and doxorubicin developed rodent, mammalian, and human MDR cell lines with Pgp overexpression. Quantitative PCR was utilised to measure Pgp expression in 39 of 60 National Cancer Institute tumour cell lines to find novel anticancer drugs. All melanomas, renal and colon carcinomas, and CNS tumour cell lines expressed Pgp. To create the H69AR multidrug-resistant version, Cole and colleagues chose the NCI-H69 human small-cell lung cancer cell line for doxorubicin resistance. This cell line was resistant to colchicine, vincristine, and vinblastine, such as other Pgp-overexpressing cell lines. Interestingly, Pg-preactive monoclonal antibodies did not detect cell Pgp. The MDR cell line contains 6 times less GSH than the parent line despite increased GSH enzyme activity [37].

Using drug-resistant cell line mRNA cDNA clones, Cole and colleagues revealed an ABC transporter gene with increased expression. After discovering more ABCC subfamily members, this protein became MRP1. In gastrointestinal, breast, renal, and haematological cancers, including AML, MRP1 is expressed. MRP1 is abundant in tiny and non-small cell lung tumours, and it is said that clinical MDR in cancer goes beyond Pgp and MRP1 [38]. To test treatment resistance, Chen and colleagues increased doxorubicin concentrations in MCF-7 breast cancer cells using verapamil, a Pgp inhibitor. MCF-7/AdrVp progenitor cells were 900-fold doxorubicin- and drug-resistant. The cell line had normal GSH and vinblastine resistance without Pgp. A 95 kDa membrane protein overexpression during doxorubicin resistance decreases when the medication is withdrawn but not when verapamil is removed [39].

Offspring inherit resistance via vertical transmission, conjugation, transduction, and transformation. Plasmids contain most resistance genes. Four strategies create a cell or organism chemotherapeutic-resistant:

Drug deactivation

Deactivation of drug is one of the most common mechanisms of resistance to antimicrobials. Bacteria can also make enzymes to inactivate the antibiotic compounds before they are able to reach biological targets. One of the classical examples is the production of β-lactamases, which hydrolyze penicillin and similar β-lactam antibiotics. In a similar manner, chloramphenicol resistance is often mediated by chloramphenicol acetyltransferase, an enzyme that chemically alters the medication and abolishes its activity. Aminoglycoside resistance may also be generated during enzymatic modification such as phosphorylation, adenylation and acetylation reactions that decrease drug binding and antimicrobial efficacy.

Medication binding site changes

Changes to drug-target sites represent a second key mechanism of resistance. Alterations in the structure of the ribosome of bacteria will lower the binding affinity for aminoglycosides and hence inhibition. Similarly, mutations in DNA gyrase and topoisomerase enzymes are often implicated in fluoroquino-

lone resistance. Moreover, many penicillin-resistant bacteria produce modified penicillin-binding proteins (PBPs), which are less responsive to β-lactam antibiotics and thus inhibit drug action.

Cancer MDR

Chemoresistance kills 90% of advanced cancer patients, and a few first-line treatment survivors develop an insensitive secondary tumor. This accelerates tumor growth after stabilization or severe relapse when treatment fails. MDR, refractory cancer, and tumor recurrence increase after long-term chemotherapy. Additionally, MDR render cancer cells resistant to structurally unrelated chemotherapeutic medicines. MDR mechanisms include reduced water-soluble drug absorption, increased xenobiotic metabolism enzyme levels, such as glutathione-S-transferase, and cell alterations that impact cytotoxic drug killing, and energy-dependent efflux of hydrophobic medicines. ABC transporters, a membrane protein superfamily, transfer hydrophobic medicines and lipids from the inner to outer leaflet of the cell membrane, increasing MDR in several malignancies [40].

Malignant cells overexpress P-gp (MDR1, ABCB1) and MRP, decreasing intracellular drug levels and hindering treatment. P-gp is the best-characterized efflux pump that mediates cancer MDR, making its targeting an intriguing MDR therapeutic. MDR need subcellular P-glycoprotein (P-gp) expression in breast, colorectal, ovarian, lung, and other cancers. Human ABCB1, the first ABC transporter, reduces drug concentration in cancer cells and makes them resistant to paclitaxel, vinblastine, and daunorubicin. Kidney, stomach, brain, and placenta contain 170 kDa membrane transporter ABCB1. To combat ABCB1-mediated drug efflux, clinical studies have employed an ABCB1 modulator and an anticancer agent. Melatonin fight MDR via chemotherapeutic synergy, research show. Melatonin increases colon cancer cell chemotherapy sensitivity by affecting P-gp expression. The effect of melatonin on colon cancer cells' doxorubicin resistance was studied. Both MLT and DOX enhanced P-gp in certain cells. Epirubicin, a first-line DLBCL therapy, fails because to MDR transporter protein overexpression, especially P-gp. Melatonin downregulates P-gp, sensitizing DLBCL cells to epirubicin, which inhibits proliferation. P-gp inhibitors are seldom licensed for cancer treatment owing to safety or effectiveness concerns, and synthetic and natural antimicrobial peptides are being tested to treat resistant bacteria [41].

A unique cancer therapy combines the antimicrobial peptide XH-14C with traditional anticancer drugs. XH-14C directly lowers ABCB1 efflux ability to reverse ABCB1-mediated MDR and boost intracellular paclitaxel accumulation without changing transporter expression or cellular location. BCRP is another vital ABC transporter. Lung, stomach, colon, liver, breast, placenta, hematopoietic stem cell, and blood–brain barrier apical membranes contain it. AML and ALL overexpress it. AML and other cancers with dysregulated ABCG2 overexpression have poor prognoses [42]. High ABCG2 expression makes cancer cells resistant to mitoxantrone, topotecan, SN-38, and doxorubicin. Several studies show ABCG2-high malignancies resist anticancer treatments [43]. Docking simulations suggest Venetoclax inhibit efflux by binding ABCG2's drug-binding pocket and ATP-binding site. New ABC transporter efflux reversal drugs are needed to improve chemotherapy [44].

Transition metal compounds are a promising MDR cancer treatment. MODULATE ROS to kill various MDR cancer cells. ROS control cancer cell death, growth, survival, and therapeutic resistance. Drug-resistant cancer cells have higher ROS and antioxidant enzymes than ordinary cells. Thus, ROS-lowering medicines make MDR cancer cells sensitive to chemotherapies. Pomegranate Akko peel and Salvia fruticosa Mill., antioxidants and antiproliferatives, overcome cancer resistance. Polyphenol resveratrol causes apoptosis and treat breast cancer MDR. MDR also result from autophagy. This self-degradation shields cancer cells against chemotherapeutics during sensitive and MDR treatment. Autophagy-induced anticancer drugs reverse MDR by killing or activating latent apoptotic pathways in MDR cancer cells. Inhibiting P-gp and PPI help fight MDR since over 50% of human malignancies modify the p53-Mdm2 pathway. p53-Mdm2 PPI inhibitors might be used to develop multitarget medicines that reduce P-gp activity to overcome tumor resistance [43].

The ABC transporters greatly influence multidrug resistance, although their significance as main factors vs secondary adaptations is unclear, and some resistant cancers have little transporter overexpression, indicating autophagy, epigenetic regulation, or immune evasion. Since in vitro MDR models fail to fully represent tumor heterogeneity and microenvironmental complexity, their therapeutic significance is sometimes challenged. These differences hinder the translation of lab results into successful treatments.

Clinical Relevance of ABC Transporters in Oncology

There is clinical evidence showing an association with ABC transporter overexpression having adverse therapeutic outcomes in various malignancies. Increased expression of ABCB1 (P-glycoprotein) occurs in breast, ovarian, colorectal, and hematological cancers and is often accompanied by decreased intracellular accumulation of chemotherapeutic agents, shorter progression-free survival, and higher rates of treatment failure [46]. In several human studies, upregulation of ABCC1 and ABCG2 was also associated with resistance against anthracyclines, taxanes, topoisomerase inhibitors, and targeted anticancer agents. Despite promising preclinical findings, clinical trials of ABC transporter inhibitors have yielded uneven results. First-generation inhibitors including verapamil and cyclosporine A, second-generation compounds such as valspodar demonstrated the capacity to inhibit drug efflux but with limitations from toxicity and pharmacokinetic interactions [47]. More recently, precision oncology approaches have shown promise towards multidrug resistance. Tumor-level molecular profiling allows pattern identification

of transporter expression and resistance-associated biomarkers, and facilitates patient stratification along with personalized treatment strategies. These advances indicate that future resistance-targeted treatment strategies will probably encompass both transporter inhibition and individualized interventions and microenvironment-targeted therapy [48], as shown in Table 2.

Table 2. Major ABC transporters involved in cancer.

Gene	Protein	Cancer Type	Drug Substrates	Clinical Significance
ABCB1	P-glycoprotein (P-gp)	Breast, ovarian, leukemia	Doxorubicin, paclitaxel, vincristine	Poor prognosis and chemotherapy failure
ABCC1	MRP1	Lung, breast, leukemia	Anthracyclines, vinca alkaloids	Multidrug resistance
ABCG2	BCRP	Breast, colorectal, leukemia	Mitoxantrone, topotecan	Reduced therapeutic response

MDR of antimicrobials

Fast MDR bacteria development due to antibiotic overuse and ineffectiveness against biofilm-related diseases (BRIs) need alternate antimicrobial agents and methods. Several causes cause MDR in bacteria. Drug-resistant genes on resistance R-plasmids accumulate in bacteria. Increasing efflux pump genes that expel several medicines produce multidrug resistance. Finally, enzyme-mediated drug degradation or chemical group transfer produce MDR. Hydrolysis kills penicillin, tetracycline, etc [49]. Drug inactivation includes acetyl, phosphoryl, and adenyl groups. Non-fermenting Gram-negative bacteria's antibiotic resistance affects worldwide healthcare. Enterococcus faecium and E. faecalis are therapeutically relevant multi-resistant Gram-positive bacteria. MDR issues and physiological functions addressed by bacterial research. Novel AMR-fighting antimicrobials are crucial. Recent studies indicate antibacterial substances. Antimicrobial peptides (AMPs) kill MDR bacteria and BRIs without resistance, making them prospective MDR-fighters. Most CF patients die from antibiotic-resistant Pseudomonas aeruginosa [50].

In silico-designed antimicrobial peptide DP7 suppresses clinical P. aeruginosa strains and biofilm development with a wide spectrum of action, and prevented 70% of acute lung infection and 50% of chronic illness bacterial colonisation. It primarily inhibited LPS and outer membrane protein gene expression and cell-wall structure. Recently, bacterial biofilm development has drawn attention. Closed microorganism biofilms produce polysaccharides, proteins, and DNA [51]. Chromosome beta-lactamase, efflux pumps, and antibiotic target molecular alterations make biofilms antibiotic- and disinfectant-tolerant. Solid-organ transplantation (SOT) patients experience colonisation or infection from MDR-E strains resistant to carbapenems and extended-spectrum-β-lactams, leading to 5-20% mortality. Recent options include phage therapy. Ecologically ubiquitous host-specific phages infect MDR bacteria. The multidrug efflux systems MexAB and MexXY's outer membrane porin M (OprM) binds to P. aeruginosa's lytic bacteriophage OMKO1. In this novel phage treatment, phages select MDR bacteria to make them antibiotic-sensitive. This medicine halt or treat antibiotic-resistant infections and increase the clinical effectiveness of MDR bacteria [52].

The emergence of extensively drug-resistant (XDR) and pan drug-resistant (PDR) Gram-negative pathogens has been a significant global health problem. Acinetobacter baumannii and Pseudomonas aeruginosa are among the most troublesome nosocomial pathogens, particularly in intensive care units, where they are associated with ventilator-associated pneumonia, bloodstream infections, and wound infections. XDR isolates remain susceptible to only one or two types of antimicrobials, while PDR strains can resist all available ones. The extraordinary capacity of these pathogens to overexpress efflux pumps, form biofilms, acquire resistance genes via horizontal gene transfer, and adapt to hostile environments accounts for a considerable proportion of treatment failure and an increased risk of dying. As a result, novel therapeutic strategies that target resistance mechanisms have emerged as an urgent clinical priority [43, 46].

Drugs that block bacterial efflux pumps

1.Phenothiazines: Inhibitors of Bacterial Efflux Pumps

Bernthsen reacted diphenylamine with sulfur in 1883 to make heterocyclic phenothiazines. After then, German physician Paul Ehrlich discovered and investigated the phenothiazine dye methylene blue for almost 20 years. Ehrlich proved the dye was antibacterial and antimalarial and could heal malaria. After almost 50 years of research, Rhone Polenc synthesised a colourless phenothiazine with neuroleptic properties in the 1950s and introduced it as chlorpromazine (CPZ) in the US and Largactil elsewhere. The dye calmed the patient, so its psychosis treatment potential outweighed its antimicrobial properties. CPZ was extensively used internationally and had high anti-tuberculosis action, but isoniazid and rifampicin were already effective, thus little interest in it as a medicine was created [53].

The persistent human pathogen Mycobacterium tuberculosis causes intracellular TB. The pulmonary macrophage does not destroy the bacteria after inhaling microdroplets of Mtb-containing sputum from an active TB patient. Thus, the person stays infected for decades, and just 5-10% develop to active

illness. K+ and Ca2+ efflux from the phagolysosome prevents human pulmonary macrophages from killing the ingested organism. Due to the outflow of K+ and Ca2+, phagolysosomal pH does not drop enough to activate hydrolases, resulting in ordinary breakdown and killing the bacteria [54].

2. Phenothiazines: Inhibitors of Efflux Pumps of Cancer Cells

The first-ever cancer cell efflux pump inhibitor, phenothiazines, suppressed cancer formation in the early 1950s. Several studies have demonstrated that phenothiazines reduce cancer from those early years. Chlorpromazine, benzo-phenothiazines, methylene blue, and toluene blue are studied. Combining methylene blue and light for tumour therapy is common. Phenothiazine anticancer compounds destroy bacteria; however, their mechanism differs per cancer tissue. These phenothiazine anticancer drugs work against cancer cells' ABC efflux pump ABCB1, rendering them susceptible to previously resistant drugs. The ABCB1 gene encodes an ATP-binding cassette ABC transporter present in many human cells. Plasma membrane-bound ABC transporters. ABC transporters have two NBFs, two substrate binding sites, and two sets of TM domains with six membrane-spanning αhelices. The plasma membrane and cytoplasm have ATP and substrate binding sites. When the substrate site touches the extruded agent, NBF sites bind ATP. The transporter conforms to transfer the agent to the plasma membrane's external side using ATP hydrolysis energy [55].

3. Bacteria Efflux Pump Activity: Hydantoins

Hydantoins regulate cell purine reserves for nucleic acid synthesis via purine catabolism. Biotechnology uses hydantoinases to produce optically pure amino acids by hydrolyzing hydantoin and 5'-monosubstituted derivatives, which metabolism requires. The nucleobase cation symport-1 (NCS1) transporters, including Mhp1 from Microbacterium liquefaciens, save nucleobases and similar chemicals. Hydantoins treat several diseases pharmacologically and biochemically. Epilepsy has been treated with phenytoin (5,5diphenylhydantoin, Dilantin) for decades. Hydantoins' fungicidal, herbicidal, anticancer, anti-inflammatory, anti-HIV, hypolipidemic, antiarrhythmic, and antihypertensive effects depend on ring replacement [56].

Inhibitors of bacterial efflux pumps also inhibit cancer cell efflux pumps. Hydantoins combat cancer. Flavonoids in the phosphatidyl bilayer change the lipid membrane and inactivate ABCB1 or other transmembrane efflux pumps. Hydantoin boosts cancer efflux pump activity, but the substituents at positions 1, 3, and 5 are responsible. Epilepsy therapy with hydantoin phenytoin does not block efflux pumps. Adding methyl or aromatic aminealkyl to phenytoin at positions 1 or 3 increased its ability to inhibit ABCB1 in T-lymphoma cells in 123 rhodamine accumulation tests. A powerful efflux pump inhibitor, 5arylidenehydantoin HY84, affects cancer cell-subsidized ethidium bromide retention in actual cells [57].

4.Trifluoromethyl Ketones: Efflux Pump Attack

The antibacterial and antimotility effects of trifluoromethyl ketones (TFKs) and their bioactive derivatives on various bacteria have been studied for years. Some TFKs only inhibit Gram-positive bacteria, whereas others inhibit Gram-negative bacteria and yeasts. Promethazine and several TFK chemicals work synergistically against microorganisms. Their technique seems to adversely impact bacteria's proton motive force. TFKs combat cancer. They haven't been tested against cancer cells' overexpressed efflux pumps. Bacteria efflux pump inhibitors also block cancer cell efflux pumps, making them promising candidates for study [58].

Challenges and Ethics

Despite breakthroughs in microbial biofilms and tumor resistance mechanisms, converting mechanistic information into useful treatments is difficult. Biology's intricacy matters. Cancer and biofilms are heterogeneous systems with several stress-responsive cell subpopulations. Because compensating mechanisms emerge quickly, targeting one pathway, such as eflux pumps, metabolic regulators, or matrix components, often has temporary advantages. Experimental models often fail to replicate in vivo architecture, oxygen gradients, and host interactions, reducing prediction accuracy [59].

Creative therapies present ethical issues. Systemic toxicity emerge from efflux pump inhibitors and metabolic modulators targeting conserved cellular pathways. Although promising, nanotechnology-based delivery options have biocompatibility and environmental problems [60]. Effectiveness and quality of life must be balanced in aggressive oncology combination treatment. Overusing or abusing new antibiotics cause resistance. Translational research should incorporate risk benefit assessments, equitable access to advanced medications, and diligent monitoring to reduce harm [61].

Limitations of Efflux Pump Inhibitors

Despite substantial attempts to develop efflux pump inhibitors (EPIs) as adjuvant treatments, numerous major hurdles prevent their clinical translation. Several EPIs target conserved transporter architecture, which affects physiological transporters in healthy organs such the liver, kidney, and blood–brain barrier, resulting in poor sensitivity. Lack of selectivity causes systemic toxicity, a major cause of clinical trial failure. Pharmacological disagreement between EPIs and co-administered medicines might impair therapeutic effectiveness or increase side effects due to variations in absorption, distribution, metabolism, and excretion [14].

Redundancy and compensating mechanisms in efflux transporter families are another concern. In both bacterial and cancer systems, inhibiting one pump, such as ABCB1 upregulate ABCC1 or ABCG2, preserving drug resistance. Many EPIs are substrate-dependent, therefore their inhibitory impact depends on the medication, limiting their practical relevance, and membrane architecture is complicated in Gram-negative bacteria, where outer membrane permeability and efflux synergy hinder inhibitor access to internal targets. Of particular significance, EPIs generally ignore non-efflux resistance

mechanisms such metabolic reprogramming, biofilm development, improved DNA repair, and tumor cell apoptotic resistance. Thus, efflux pump inhibition seldom restores drug sensitivity. Preclinical effectiveness sometimes relies on simplistic in vitro models that don't fully represent the tumor microenvironment or biofilm complexity, resulting in poor clinical prediction [62].

Despite promising preclinical results, the clinical translation of efflux pump inhibitors in the clinic is still largely unsuccessful. Several first- and second-generation inhibitors also induced intracellular drug accumulation in vitro but many failed in clinic due to systemic toxicity, poor selectivity, unfavorable pharmacokinetic interactions, and the activation of compensatory resistance pathways. In addition, tumor heterogeneity and the complexity of the tumor microenvironment frequently reduce the effectiveness of transporter-targeted strategies. Inhibition of efflux pumps alone is therefore unlikely to effectively combat multidrug resistance, and this approach must be complemented and paired with therapies targeted at complementary resistance mechanisms [63], as shown in Table 3.

Table 3. Major efflux pump inhibitors.

Compound	Molecular Target	Mechanism	Development Stage	Limitation
Verapamil	ABCB1	ATP-dependent efflux inhibition	Clinical	Cardiotoxicity
Cyclosporine A	ABCB1	Competitive inhibition	Clinical	Drug interactions
Valspodar	ABCB1	Second-generation inhibitor	Clinical trials	Pharmacokinetic issues
Tariquidar	ABCB1/ABCG2	Potent transporter inhibition	Clinical trials	Limited efficacy
Elacridar	ABCB1/ABCG2	Dual inhibition	Preclinical/Clinical	Bioavailability concerns

Future Perspectives

Research should emphasize integrative, systems-level methods over route targeting. Biofilm and tumor resistance subpopulations will be mapped by transcriptomics, metabolomics, and spatial proteomics. Therapy exploits similar regulatory nodes. Parallel advancements in nanomedicine and smart drug delivery platforms overcome physical and biological penetration barriers. Stimuli-responsive carriers that release drugs in hypoxic or acidic settings seem promising. Predicting treatment effects requires physiologically relevant models, such as organoids and 3D biofilm tumor analog systems. AI-designed dual-purpose drugs targeting conserved survival pathways discovered faster.

Conclusion

Drug resistance, not genetics, is broad and dynamic, resulting from synergistic change at molecular, metabolic, and structural levels. Even with potent drugs, efflux pumps lower internal drug concentrations, and biofilms and tumor microenvironments form defensive niches that block therapeutic penetration. Microbial and cancer systems share pathways that show resistance is a community survival strategy and transporter function, extracellular matrix, and metabolic flexibility may be targeted. Experimental efflux pump inhibitors and nanocarrier systems are promising, but toxicity and pharmacokinetic complexity prevent clinical translation. Dual-target inhibitor and stimuli-responsive delivery studies will expand uses. Multi-omics profiling and physiologically accurate 3D models should predict therapeutic success for future study. This research shows that transporter inhibition alone is not enough to eliminate multidrug resistance (MDR), which requires multidisciplinary efforts.

Author declarations

Author Contribution

A.W.A. conceived the review concept, designed the study framework, performed the literature search, analyzed and interpreted the literature, drafted the manuscript, critically revised the intellectual content, and approved the final version of the manuscript.

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Data Availability Statement

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Ethical Approval

Ethical approval was not required for this study because this article is a narrative review based exclusively on previously published literature and does not involve human participants, animals, or identifiable patient data.

Consent for Publication

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