Research Paper

From Antibiotics to Cover Repurposing Strategies to Develop New Anticancer Drug

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ABSTRACT

Antibiotics, which were originally intended to treat bacterial infections, have incredible potential for repurposing as anticancer treatments due to their known safety profiles, cost-effectiveness, and ability to target cancer cell vulnerabilities. This review investigates how antibiotics combat proliferation, metastasis, and drug resistance by exploiting similarities between bacterial and cancer cell processes, such as mitochondrial protein synthesis inhibition (doxycycline, azithromycin), DNA damage via intercalation (doxorubicin, bleomycin), ROS overload resulting in ferroptosis, cell cycle arrest, and anti-angiogenic effects. Cancer continues to be a global epidemic, with 19 million new cases and 10 million deaths expected in 2020 alone, compounded by resistance mechanisms that render existing treatments insufficient. Repurposing speeds up development (6.5 years vs. 13-15), lowers expenses ($200 million vs. $2-3 billion), and increases approval rates (30% vs. 11%). Tetracyclines, for example, target cancer stem cells while also acting on bacteria-induced cancers such as H. pylori stomach tumors and Salmonella gallbladder cancer. Advanced techniques, such as network pharmacology, organoid models, molecular docking, and AI/ML, help to identify candidates. Antibiotics combat infection-related oncogenesis by neutralizing toxins, reducing inflammation, and working in tandem with chemotherapy and immunotherapy. This method provides rapid clinical translation for resistant "cold tumors" such as pancreatic and glioblastoma, converting existing medications into adaptable bactericidal-cancer-killing agents while overcoming ESKAPE pathogen threats that are expected to take 10 million lives each year by 2050.

Keywords: Drug repurposing, antibiotics, anticancer agents, bacteria-induced cancer, mitochondrial inhibition, DNA damage, ROS generation, doxycycline, anthracyclines, Helicobacter pylori, Salmonella typhi.

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1. Introduction:

Antibiotics were originally developed to treat bacterial infections, but they have also shown great potential for repurposing as anticancer agents [1]. They are safe, already tested on humans, cheap to develop, and can target cancer cell processes efficiently[2]. Cancer plays a major role in health problems worldwide, with uncontrolled cell proliferation, genomic instability, and metastasis to other parts of the body [3]. In 2020 alone, there were about 19 million new cases and 10 million deaths from it [4]. Many drugs can not work properly because cancer cells develop complex resistance mechanisms, due to which there is a need for alternative therapies [5]. Repurposing uses existing drugs instead of starting from scratch, skipping slow steps like finding target identification, and going directly to clinical trials [6]. It's faster, cheaper, and safer because we already know how the drugs work in the body [7]. Examples like metformin (from diabetes to cancer treatment) and aspirin prove it works in real life, with less chance of failure than brand-new drugs [8]. Bacterial genomes and eukaryotic mitochondria enable antibiotics to disrupt cancer cell DNA or RNA synthesis, trigger apoptosis, slow growth, and stop cells from changing shape to spread [9]. Examples include anthracyclines like doxorubicin, which treat blood cancers and breast cancer via DNA intercalation, and tetracyclines like doxycycline targeting cancer stem cells [10]. Antibiotics are being repurposed through computer scans for unanticipated cancer effects, lab testing drugs like ciprofloxacin and salinomycin, and pairing the drugs with chemotherapy to overcome resistance [11]. They fight cancers caused by bacteria (like H. pylori stomach tumours) by preventing inflammation and stopping tumour growth. Cancer is the second most common cause of death in the world due to either targeted or non-targeted drug resistance, despite advances in targeted therapies [12]. Repurposing will exploit drugs already approved for use that have, on average, over six other off-targets [13]. The safety record of these

drugs is known, and repurposing is less costly and over a shorter timeline than developing new entities [14]. Antimicrobials (antibiotics, antivirals or antifungals, anthelmintics or antimalarials) may have anticancer activities in unexpected ways, such as via off-targets, synergy with chemotherapy and benefits in immunosuppressed patients [15]. A dual-action approach against bacteria-induced cancer (Cancer Pathogenesis and Therapy, 2025) highlights bacteria-induced cancers as important health threats [16]. This is because these cancers are associated with chronic infections. These infections arise mostly from pathogens like Salmonella typhi, Helicobacter pylori, and Escherichia coli [17]. Bacteria cause cancers of the gallbladder, gastric, kidney, and bladder through biofilms, toxins (CagA, typhoid toxin), inflammation, DNA damage, and disruption of JAK/STAT3, MAPK pathway current anticancer drugs are inadequate [18]. At the same time, the new drug discovery takes about 8-10 years with a frequent failure rate [19]. Drugs such as azithromycin and ciprofloxacin enhance chemo efficacy against infection-related cancers [20]. Reinvention of anti-cancer drugs as new anti-infective agents [21]. It is the first official CDC report that details that several drugs like alkylating agents such as mitomycin C cisplatin, antimetabolites such as 5-fluorouracil, gallium nitrate show promising antibacterial activity against the multidrug-resistant ESKAPE pathogens [22]. Anti-cancer agents target common characteristics present in cancer cells and bacteria, like rapid proliferation and high metabolism [23]. One example is gallium nitrate, which may disrupt iron metabolism in P. aeruginosa and was effective in cystic fibrosis trials [24]. The process of drug repurposing enables cancer treatment development because it uses existing non-cancer medicines to create new treatment options, which solve both the expensive nature and slow development times, which take from 10 to 17 years and the high failure rate, which reaches 90 per cent in traditional drug creation processes [25]. The repurposed agents from multiple drug classes including anthelmintics which include mebendazole and flubendazole that block tubulin and induce apoptosis and antivirals which include ritonavir and nelfinavir that block Akt/STAT3 and antibiotics which include doxycycline that stops MMPs and metastasis and antifungals which include itraconazole that stops Hedgehog/mTOR and antimalarials which include chloroquine and artesunate that induce ROS/apoptosis and anti-inflammatories which include aspirin and celecoxib that control COX/NF-κB show their ability to stop cancer cell growth and induce cell death and stop blood vessel formation and change immune system activity in various cancer types which include breast cancer and colon cancer and prostate cancer and glioblastoma [26]. The strategy enables faster clinical development by leveraging known safety information, thereby reducing costs and focusing on common cellular pathways, including Wnt/β-catenin, PI3K/Akt, and autophagy [27]. It also supports combination treatment strategies for challenging tumours, as evidenced by positive results from preclinical and clinical studies [28]. While receiving chemotherapy, many of the. The body's neoplasm grows resistant to the drug. In the area of. The issue of drug resistance in cancer is quite critical Figure 1.

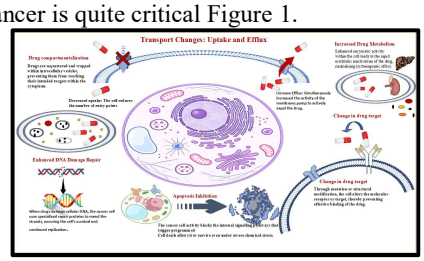

Fig 1. Mechanism of cancer drug resistance.

2. Concept and Importance of Drug Repurposing

- Repositioning existing drugs for new therapeutic targets.

  Drug repurposing, also called repositioning, is defined as the identification of new indications from existing drugs, as well as the application of the newly identified drugs to the treatment of diseases other than the drug's target disease [29]. One of the well-known examples of drug repositioning is the use of Sildenafil (also known as Viagra), developed by Pfizer as a PDE5 inhibitor for coronary artery disease treatment in the 1980s, which exhibited penile erections as a secondary effect during hypertension and angina trials [30, 31]. After failing Phase II trials for angina, the drug was repurposed for erectile dysfunction and approved by the FDA in 1998, reaching blockbuster status. Thalidomide, marketed by Grünenthal as a sedative for morning sickness treatment in 1957, caused severe congenital disorders in over 10,000 children in 46 countries, prompting its withdrawal [32]. Thalidomide, a drug once thought to have caused irreparable damage, showed its ability to inhibit cancer cell formation by inhibiting angiogenesis and was approved by the FDA for multiple myeloma treatment in combination with dexamethasone in 2006 [33].

2.1 Benefits of Drug Repurposing

The traditional de novo drug discovery process is very expensive, costing $2-3 billion, and very slow, taking 13-15 years. There are also very high failure rates, around 90%, and very low drug approval rates, around 11%. These statistics are even worse for neurodegeneration. The drug repurposing of Phase I-tested compounds increases the drug approval rate to 30%, reduces the drug safety risks, and reduces the drug development period to 6.5 years and the drug development costs to 200 million dollars. The drug regulatory dossier approach minimises drug studies by relying on pre-existing data. This approach would be very useful for urgent drug needs, such as rare ones. [34, 35]

2.2 Hurdles Facing Drug Repurposing

However, there are hurdles related to intellectual property rights and commercialisation when it comes to repurposing drugs, as it is very difficult to re-patent known drugs in the absence of new therapeutic insights. There are issues with data access due to commercial confidentiality, although government programs in developed nations cover costs in public clinical trials. Scientifically, in vitro studies are not always predictive of in vivo outcomes due to the complexity of diseases, pharmacokinetics, and off-target effects, as seen with hydroxychloroquine in COVID-19 trials. The success of a drug also depends on mechanistic validation, safety of doses, and achievable concentrations. [35]

3 Approaches in Repurposing

- **Network Pharmacology**

Network pharmacology introduces a systems-level paradigm in drug discovery and repurposing, moving beyond the conventional "one drug–one target" model to embrace multi-target strategies that integrate biology, pharmacology, and computational tools for mapping complex drug-target-disease networks. This approach facilitates drug repurposing by leveraging existing drugs' polypharmacology, offering a faster, cost-effective alternative for complex diseases like cancer, psychiatric disorders, and infections, as demonstrated in COVID-19 virtual screenings and oncology cases such as arsenic trioxide. Key methods include network construction from multi-omics and GWAS data, topological analyses, and AI-enhanced predictions via public databases, enabling precise modulation of disease pathways. Challenges persist, including data gaps and regulatory hurdles for multi-target agents, yet advances in dynamic modelling and machine learning promise to enhance precision medicine applications. Overall, network pharmacology not only elucidates synergistic interactions but also accelerates clinical translation, aligning with sustainable innovation in repurposing scaffolds such as thiazolidinediones for anticancer applications. [36]

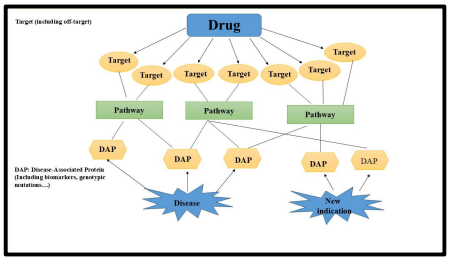

Fig 2. Network Pharmacology: Systems-Level Drug Repurposing for Multi-Target Cancer Therapies

- **Experimental approach: Organoid and Tumoroid Models in Cancer Research**

Organoids are self-organising 3D structures that scientists create by culturing stem cells, progenitor cells and tumour tissue in specialised extracellular matrix-based gel environments. Tumoroids—a type of cancer organoid—closely mimic the original tumour's architecture, function, genetics, mutations, and drug responses. The models show better performance than conventional 2D cell lines because they maintain patient-specific characteristics, which make the models suitable for fundamental research and initial stages of drug development. The study found that patient-derived organoids (PDOs) developed from non-small cell lung cancer (NSCLC) tissues exhibited less responsiveness to cisplatin than the tested cell lines, which demonstrated important resistance mechanisms through their diminished DNA repair capabilities. The research used patient-derived organoids to test different drug combinations and discover new treatment options for patients with gastrointestinal cancers. The researchers successfully predicted treatment results for patients with KRAS-mutant microsatellite-stable metastatic rectal cancer who underwent liver resection and neoadjuvant chemotherapy. Edited responses in hepatocellular carcinoma (HCC). and replicated resistance in oesophageal squamous cell carcinoma. The ability of tumoroids to mimic the complete organ structure and gene expression

patterns and essential organ functions makes them an effective tool for drug screening (Fig. 3). The research includes two studies that test SMAC mimetic LCL161 in liver-metastatic rectal cancer and CDK7 inhibitor YPN-005 in small cell lung cancer (SCLC) tumoroids. The combination of breast cancer patient-derived organoids and tumour-specific T cells in the high-throughput screen discovered three epigenetic drugs (BML-210, GSK-LSD1, and CUDC-101) that produced powerful antitumor results through immune system cooperation. The administration of atorvastatin to glioblastoma organoids, together with endothelial cell research, showed that the drug reduced VEGF, CD31 and Bcl-2 protein levels, which resulted in decreased blood vessel growth. The 2023 study demonstrated that PDO predictive capabilities improved because researchers included multi-omics data, which included single-cell RNA sequencing data, in their research. The adoption of immune cell co-culture systems has improved pancreatic cancer PDOs' ability to predict checkpoint inhibitor treatment effectiveness because these systems better recreate tumour microenvironment conditions. Tumoroids excel in precision oncology but face heterogeneity, missing TME elements, vascular issues, and standardisation hurdles. Advances like bioprinting, biobanks, and AI-multi-omics promise enhanced utility [37].

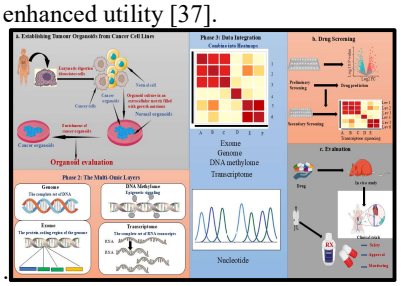

Fig 3. Tumoroid Models: Revolutionising Cancer Research from Bench to Precision Medicine

- **Computer-Aided Approaches for Identifying Repurposed Anticancer Drugs**

Genome-wide association studies are a method used to find genetic variations that play a significant role in drug repositioning. They reveal a biological understanding of how complex diseases work that can help in identifying compounds appropriate for repurposing. Several variants linked with clinically relevant phenotypes, shedding light on genes, pathways, and genetic overlap between different traits, have been identified by GWAS. Genome-wide association studies typically focus on common variants for their power and ease of imputation. However, the combined effect of multiple common variants greatly adds to overall trait heritability. The statistical genetics community has developed advanced ways to link GWAS with other 'omics' data sets, allowing for medication repurposing prospects. Cheng et al. used DNA/RNA sequencing to uncover new therapeutic targets and repurpose current medications to treat various diseases by specifically targeting individualised disease modules. For repurposing drugs, Cheng et al. give a novel algorithm called the genome-wide positioning systems networks(GPSnet). Their approach involves mapping disease modules discovered from sequencing data to the human protein-protein interactome network. GPSnet's ability to accurately analyse sequencing data from 5000 patients across 15 cancer types from The Cancer Genome Atlas is demonstrated. Predicting pharmacological responses and identifying potential new uses for 140 approved medications. The experimental validation of ouabain, a drug approved for treating cardiac arrhythmia and heart failure, shows promising anti-tumour actions in lung adenocarcinoma by targeting the HIF1α/LEO1-mediated cell metabolism pathway [25].

- **Structure-Based Repurposing**

Molecular docking is a structure-based drug design technique that uses computer resources efficiently and quickly evaluates millions of molecules. Several commercial molecular docking tools, such as CovDock, FLEXX, GOLD, and ICM-Pro DOCKTITE, Molecular Operating Environment (MOE), MacDOCK, CovalentDock, and AutoDock 4 are tools for drug discovery and repurposing. Several investigations have indicated that docking can be utilised to repurpose drugs. Shaikh et al. simulated 112 chemotherapeutic agents against 18 validated kinase targets from nine cancer types. Several Molecular modelling tools, MOE, Cresset-Flare, AutoDockVina, GOLD, and GLIDE were utilised for comparative analysis. Drugs such as leucovorin, nilotinib, ellence, thalomid, and carfilzomib are effective against several cancer targets. A library of new compounds was created using existing drug

scaffolds, with 20 prioritised for drug-like characteristics. AutoDock Vina showed good results for docking these compounds against cancer-related proteins. Target-focused compound libraries are collections of compounds that interact with certain protein targets or families to uncover prospective therapeutic candidates during screening. These libraries are designed using structural information on the targets. They can be identified using chemogenomic models utilising sequence and mutagenesis data, as well as information on ligand interactions. Libraries can be a great resource for drug repurposing. For example, Gan et al. developed DrugRep, an automated method for virtual screening based on receptors and ligands. Three drug libraries (approved, experimental, and traditional Chinese medicine) were gathered for this study. DrugRep utilises novel methods like CurPocket for receptor-based screening. Curvature factors are calculated to properly predict protein-ligand binding sites. LigMate and FitDock approaches are used for ligand-based virtual screening, resulting in higher enrichment power compared to previous methods [25].

- **Role of Machine Learning, Artificial Intelligence, and Deep Learning in Drug Discovery**

  Machine learning (ML), artificial intelligence (AI), and deep learning (DL) use computational algorithms to examine vast datasets and detect patterns. This allows researchers to make predictions and judgments without explicit programming. Machine learning algorithms aid in drug discovery by identifying and validating novel therapeutic targets, screening compounds, designing drugs, discovering biomarkers, stratifying patients, and optimising clinical trials. While these are not explicitly related to drug repurposing, the insights gained can help identify existing pharmaceuticals with potential repurposing options for cancer treatment. ML, AI, and DL can be used for literature searches, EHR-based approaches, and drug-target interactions. ML, AI, and DL are used at different stages of drug discovery and development, such as drug repurposing for cancer treatment. Natural language processing (NLP) is used to examine PubMed abstracts for evidence of non-cancer medications' potential anticancer effects. Zeng et al. created RetriLite, a framework that uses natural language processing and domain-specific knowledge. skills to search through documents and obtain relevant information. This approach identifies papers that evaluate the effectiveness of combination medicines in clinical or preclinical investigations. In early tests, RetriLite revealed great effectiveness with an F1 score = 0.93. Further validation aimed at discovering compounds that enhance antitumor potency using poly (ADP-ribose) polymerase inhibitors, RetriLite achieved a 95.9% true positive rate and 97.6% accuracy in distinguishing clinical and preclinical studies. Interobserver assessment validated the user consensus. RetriLite's proven tool is useful for creating domain-specific information retrieval and extraction systems, providing users with detailed metadata tags and keyword highlighting for efficient discovery in the combination therapy domain. EHR datasets provide valuable longitudinal and pathophysiology data to support drug repurposing initiatives. Ryu et al. conducted a major study on monoclonal gammopathy of uncertain significance (MGUS). A non-cancerous haematological disorder that might progress to malignant diseases like multiple myeloma. The Mayo Clinic's MGUS database of 16,752 patients diagnosed between 2000 and 2021 was evaluated using machine learning and EHR data. By combining this data with medication and comorbidity information from the EHR, they investigated 21 pharmacological classes of interest. They used the XGBoost module to build a primary Cox survival model and conduct sensitivity analysis on patient subgroups. The study found that some drugs, such as beta-blockers, immunosuppressants, multivitamins, non-coronary NSAIDS, opioids, proton pump inhibitors, statins, and vitamin D supplements, can lower the risk of MGUS progression. Novel computational tools, such as time-resolved screening, can be used to research drug repurposing. Using PubMed Identifiers (PMID), several time-resolved networks that represent knowledge up to specified dates can be created. Time-resolved networks can be tested for computational relocation by training on known indicators during the network's time period and testing on permitted indicators after that period, simulating real-world conditions more closely [25].

3. **Antibiotics as Potential Anticancer Agents.**

   Antibiotics combat cancer because they target tumour cells, which possess bacterial

weaknesses that allow the drugs to disrupt their energy requirements and uncontrolled development [38].

3.1 Mechanistic Basis: How Antibiotics Target Cancer Vulnerabilities.

- **Inhibition of mitochondrial protein synthesis:**
  Cancer cells depend on their mitochondria because these organelles serve as their energy sources, and mitochondria evolved from ancient bacteria, which still maintain their original bacterial ribosomes, membrane structures and protein systems. Cancer stem cells lose their energy supply because the antibiotics tetracyclines (doxycycline) and macrolides (azithromycin) bind to mitochondrial ribosomes, which stop protein production, leading to the destruction of 50-70% of breast CSCs in preclinical studies [39].
- **DNA intercalation:**
  Certain antibiotics work against cancer cells by attacking their DNA through two different mechanisms. Doxorubicin and other anthracyclines intercalate into DNA, which prevents transcription and replication, while they also stop topoisomerase II from unwinding DNA during cell division. The disruption of this process stops non-small cell lung cancer (NSCLC) cells from growing normally. Bleomycin induces DNA damage through free radical production, which creates breaks in DNA strands that result in cell death [40].
- **Cell Cycle Arrest Across Phases:**
  Antibiotics can help to control the uncontrolled growth of cancer cells by blocking their progress through various phases of the cell division process. Cancer cells normally divide continuously without proper regulation, but certain antibiotics can block this process at specific checkpoints. Chloramphenicol prevents cancer cells from progressing through the G1 phase to the S phase, which is the DNA synthesis stage. The cells cannot replicate their DNA, which prevents them from entering the next stage of cell division. Linezolid stops cells from moving between the G2 phase and the M phase, which is the stage where cells prepare for mitosis. The cell cycle interruption leads to reduced proliferation in a large number of leukaemia cells. Salinomycin targets cancer stem cells that exist in their dormant state during the G0 phase because these cells usually do not respond to standard treatments. The drug decreases the levels of crucial stemness proteins SOX2 and OCT4, which help cells maintain their ability to self-renew and survive. Salinomycin decreases these protein levels, which causes cancer stem cells to die and may reduce the risk of tumour recurrence [41].
- **Multi-Pathway Disruption:**
  Antibiotics can stop cancer development by attacking three different pathways which control how cells survive, how tumours develop blood vessels and how cancer cells spread their signals throughout the body. The main mechanism of this process involves two processes that lead to cell death through apoptosis induction. Antibiotics create disturbances in the normal function of pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins. The disturbance results in cell death, which triggers the activation of three enzymes, caspase-3, caspase-8 and caspase-9, which play a role in the apoptotic process. The agents also cause increased p53 expression, which functions as a crucial tumour suppressor protein responsible for DNA damage detection and apoptosis promotion. Tetracycline antibiotics show anti-angiogenic properties, which stop tumours from forming new blood vessels that deliver essential nutrients and oxygen for their growth. The process results in decreased tumour blood vessel development because it reduces the production of vascular endothelial growth factor and matrix metalloproteinases. Antibiotics work as cancer prevention agents by stopping cancer cells from undergoing epithelial–mesenchymal transition, which results in their ability to move and invade other areas. The agents block essential signalling pathways which protect cells from danger, thus leading to decreased tumour development, resistance and metastasis [42].

Table 1. Repurposing Antibiotics as Anticancer Agents: Mechanisms and Therapeutic Potential.

Mechanism	Example Antibiotics	Effect on Cancer	References
Mitochondrial inhibition	Doxycycline, Azithromycin	Cancer stem cells need energy. If mitochondria are blocked	[43]

		, then the cell does not get energy, and ultimately, the cell dies.	
DNA damage	Doxorubicin, Bleomycin	If DNA get damaged, cancer cells can not grow and multiply.	[44]
ROS overload	Levofloxacin, Amoxicillin	Due to oxidative stress, Ferroptosis	[45]
Cell cycle arrest	Linezolid, Salinomycin	Stopping the cell cycle at G2/M phase, the cell can not divide, and ultimately, the cell dies.	[46]
Angiogenesis	Tetracyclines	Cancer cells need a blood supply to grow if it is blocked due to starvation cell dies.	[47]

The FDA-approved safety profiles of Repurposing Edge allow for quick clinical testing, which results in 70% cost reductions, and their combination treatments successfully treat pancreatic and glioblastoma "cold tumours" resistant to standard therapies. The dual function of the system transforms internal tumour microbiota through its two mechanisms, which enhance the effects of immunotherapy [48].

4. Antibiotics targeting Bacteria-Induced Cancers

Cancer causes abnormalities in cell development, mutations, and DNA damage. Bacteria cause oncogenesis by affecting the host's immune system and changing cells cycle and induce persistent inflammation. Bacterial infections, including gallbladder infections, have been linked to several forms of cancer. Cancer of the urinary bladder, lung, or kidney. We focused on gallbladder, stomach, kidney, and bladder oncogenesis due to their strong correlation with bacterial infections [16]. (Figure and Table)

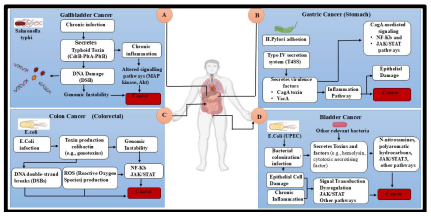

Fig 4. Bacteria-caused cancer pathways. Typhoid toxin, produced by Salmonella, can cause DNA damage and disrupt signalling pathways, leading to gallbladder cancer development. Helicobacter pylori uses adhesion factors such as BabA, sSabA, OipA, and AlpA/B to attach to the gastric epithelium and release CagA, which contributes to gastric cancer growth. (C) Kidney cancer: binding of the FADA to E-cadherin disturbs cellular integrity. and increases the risk of developing kidney cancer. Bladder cancer is caused by chronic inflammation caused by bacterial toxins, which disrupts the JAK/STAT3 signalling pathway and increases interleukin levels. Akt: Protein kinase B; Alp: Adherence-associated lipoprotein; BabA: Blood group antigen-binding adhesion. CagA: Cytotoxin-associated gene A, Cdt: Cytolethal distending toxin; MT (epithelial-mesenchymal transition); FADA (fatty acid synthase-associated domain); F. nucleatum: Fusobacterium nucleatum, H. pylori, IL, JAK, MAPK, Plt, Src homology2, SHP-2, STAT, T4SS, TMAO, and VacA are acronyms for various proteins.

Table 2.

S. no	Cancer Type	Associated Bacteria	Oncogenic mechanisms	References
1.	Gall bladder Cancer	Salmonella typhi	Production of bacterial toxins, gallstone formation, chronic inflammation, and cytolethal distending toxin, leading to DNA damage	[49]
2.	Kidney Cancer	Streptococcus, Romboutsia, Peptostreptococcaceae, Allobaculum	Promotion of inflammation, gallstone-related effects (if applicable), genotoxic DNA lesions, and disruption of cell signalling pathways	[50]
3.	Bladder Cancer	Streptococcus, Aerococcus, Sphingobacterium, Aerococcus, Pseudomonas	Induction of inflammation via N-nitrosamines, polyaromatic hydrocarbons, oxidative free radicals, protease enzymes, and alterations in DNA integrity plus cell signalling	[51]

5.1. Gastric cancer (Stomach cancer)

Gastric cancer is the fourth greatest cause of cancer-related deaths globally, resulting in around 1,000,000 new cases and 700,000 fatalities each year [52]. The main risk factor for stomach cancer is Infection with H. pylori [53]. This Gram-negative microaerophilic bacterium only colonises the stomach epithelium [54]. H. pylori is the most common bacterial infection worldwide and is classed as a Group 1 carcinogen by the World Health Organisation (WHO) [55]. Infection with H. pylori causes chronic non-atrophic gastritis, which can lead to intestinal metaplasia, dysplasia, and gastric cancer [56]. Asymptomatic H. pylori infections can cause problems, including peptic ulcers, which can progress to cancer [57]. The bacterium's pathogenicity stems from its ability to penetrate the gastric mucosa via flagella, allowing it to avoid the acidic environment of the stomach [58]. H. pylori produces urease, which neutralises gastric

acidity and creates a favourable environment for survival [59]. H. pylori adheres to the stomach epithelium through particular adhesion factors, such as (BabA) blood group antigen-binding adhesin, (SabA) sialic acid-binding adhesin, outer inflammatory protein A (OipA), and adherence-associated lipoproteins (AlpA/B) [60]. These outer membrane proteins link to receptors on epithelial cells, firmly anchoring the bacterium to the host. H. pylori secretes virulence proteins, including cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), that play a vital role in the development of gastric cancer [60]. The cagA gene is responsible for injecting CagA protein into host epithelial cells through the type IV secretion system (Cag T4SS) [61]. CagA is phosphorylated by host tyrosine kinases, including Src and Abl, and interacts with important host proteins, including SH-2. These proteins include SHP-2, Grb2, and Crk [61]. These interactions activate carcinogenic signalling pathways, including Ras and MAPK, which promote uncontrolled cell proliferation and cancer [62]. T4SS helps transport VacA toxin into host cells. VacA creates cytoplasmic membrane pores that allow it to enter endosomes and mitochondrial endocytic vesicles [63]. VacA inhibits mitochondrial function by releasing cytochrome c, leading to apoptosis. CagA and VacA's dysregulation of cell death and proliferation contributes to stomach cancer growth. CagA and VacA promote chronic inflammation by releasing pro-inflammatory cytokines such as IL-1β and IL-6. IL-8 and TNF-α induce oxidative stress and DNA damage [64]. These occurrences can potentially lead to the development of stomach cancer. H. pylori's multiple virulence mechanisms, including evasion of the gastric environment, activation of oncogenic signalling, and apoptosis, highlight its crucial involvement in gastric cancer [65].

5.2. Gallbladder cancer

The gallbladder is a pear-shaped structure found underneath the liver [66]. The gallbladder facilitates the release of bile into the small intestine, despite not producing it. At the Same time, bile can be stored [67]. When food enters the small intestine, the gallbladder releases bile to aid digestion [68]. Bacterial infections like typhoid, E. coli, and gallstone disease can cause chronic diseases in the gallbladder, leading to oncogenesis [69]. Typhoid infections and gallstones are the leading causes of gallbladder cancer [70]. Salmonella typhi causes typhoid infections in 11-12 million individuals each year, which enter the body through contaminated food and water and reach the small intestine [71]. After crossing the small intestine's epithelial layer, it enters the microphase (phagocytic and non-phagocytic cells) and moves to numerous organs, including the liver and gallbladder. Within the gallbladder, Salmonella typhi infections last a long time and are asymptomatic. Salmonella typhi generates harmful compounds that cause cancer, including nitro-chemicals, pertussis toxin (Plt), effector proteins, and typhoid toxin. The cytolethal distending toxin (Cdt) is encoded by three genes: CdtA, CdtB, and CdtC. Cytolethaltoxins cannot enter host cells' DNA; they join with Plts (Plts A and B) to generate a unique triplet (CdtB-PltA-PltB) that enters the cell. As a result, it damages host cell DNA and alters cell cycles.

Furthermore, Salmonella outer protein E (SopE), Salmonella outer protein B (SopB) and protein E2 (SopE2) improve bacterial viability in host cells by altering the MAP kinase and Akt pathway. These events promote proto-oncogene expression. Typhoid toxins in combination with bile juice create a toxic environment that directly affects the gallbladder epithelium, leading to increased inflammation. These events may cause normal gallbladder cells to become malignant. Gallstones in the gallbladder can promote bacterial colonisation and biofilm formation, leading to potential health issues. There is a direct association with oncogenesis [16].

5.3. Kidney cancer

Kidney cancer is a severe health concern for humans, with two main types: renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) [72]. Kidney cancer is estimated to cause 1.8% of cancer-related deaths worldwide, underscoring its significant influence on human mortality (GLOBOCAN2020 database) [73]. Kidney cancer can be caused by various reasons, including bacterial infections, genetic predispositions, and cystic kidney disease [74]. Some bacterial species, such as Comamonadaceae, Streptococcus, Romboutsia, Peptostreptococcaceae, Allobaculum, and Candidatus Aquiluna rubra, have been linked to kidney cancer onset and progression [75]. However, recent evidence suggests that malignant

kidney tissues may harbour a diverse microbial population. Fusobacterium nucleatum, Blautia, and Streptococcus are commonly found in RCC and have a role in oncogenesis by changing signalling pathways and causing DNA damage. F. nucleatum has been shown to stimulate cell proliferation in colorectal cancer via binding to E-cadherin's fatty acid synthase-associated domain (FADA). E-cadherin plays a crucial role in cell adhesion and epithelial integrity. It creates adherent junctions and works with cytoskeletal components to maintain tissue structure. FADA reduces E-cadherin function, leading to epithelial-mesenchymal transition and interactions in the tumour microenvironment. This compromises epithelial integrity and promotes cancer growth and metastasis. This process promotes cancer cell detachment and migration, improves interactions in the tumour microenvironment, and favours tumour development and metastasis. F. nucleatum influences molecular pathways involved in colon cancer development. Bacterial metabolites such as p-cresol sulfate, indoxyl sulfate, phenylacetylglycine, trimethylamine oxide (TMAO), and phenyl sulfate promote kidney cancer by causing inflammation and generating pro-inflammatory cytokines.33 These cytokines increase DNA damage and promote tumour formation. TMAO has been linked to accelerated renal tubular interstitial fibrosis and kidney disease.34 However, the exact processes of bacteria-induced kidney cancer are still unclear. More research is needed to better understand these mechanisms and identify potential treatments for bacteria-induced kidney cancer in the elderly [16].

5.4. Bladder cancer

Bladder cancer is the fourth biggest cause of cancer in males globally [76]. In 2020, there were an anticipated 614,000 new cases and 220,000 deaths worldwide [77]. Bladder cancers are classified as either non-muscle-invasive (NMIBC) or muscle-invasive (MIBC) [78]. The main symptom of bladder cancer is microscopic inspection or hematuria.36 In bladder cancer, 75% are restricted to the mucosa (NMIBC), and 25% are MIBC [78]. Bacterial infections in the urinary bladder, including Streptococcus, Anaerococcus, Aerococcus, and Pseudomonas, can induce significant inflammation and lead to oncogenesis. According to one study, Sphingobacterium and Aerococcus can serve as indicators for urinary infections [79]. These bacteria create enzymes and harmful compounds such as N-nitrosamines, polyaromatic hydrocarbons, free radicals, and proteases[80]. Bacterial proteases damage host tissues and cause inflammation. Chronic inflammation triggers the generation of ROS and bacterial toxins, including N-nitrosamine [80]. These mechanisms cause the secretion of IL-6 and IL-10, which limit the immune system's capacity to target and kill cancer cells. This increases cancer risk. Furthermore, IL-6 and IL-10 disturb the cell cycle and activate the JAK/STAT3 signalling pathway [81]. The route increases cancer cell proliferation while inhibiting apoptosis, leading to tumour development [82]. These events cause DNA damage in host cells and interrupt the cell cycle, raising the risk of oncogenesis.40 A study found that few cancer patients exhibit significant production of cyclooxygenase, which is triggered by bacterial infections [16]. 41 Bacteria play a significant role in the development of bladder cancer by regulating tumour growth through cyclooxygenase activity. Furthermore, IL-6 and IL-10 disturb the cell cycle and activate the JAK/STAT3 signalling pathway [83]. The route increases cancer cell proliferation while inhibiting apoptosis, leading to tumour development [84]. These events cause DNA damage in host cells and interrupt the cell cycle, raising the risk of oncogenesis [85]. A study found that few cancer patients exhibit significant production of cyclooxygenase, which is triggered by bacterial infections. Bacteria play a significant role in the development of bladder cancer by regulating tumour growth through cyclooxygenase activity [16].

5. Need for Repurposing Antibiotics as Anticancer Agents

Drug repurposing is a promising approach to overcome problems in traditional drug discovery [86]. Creating new medications is a time-consuming and expensive procedure with poor success and high failure rates [87]. Drug repurposing uses existing medications for new therapeutic purposes and provides several benefits [88]. This method focuses on adapting "old drugs" for new therapeutic applications [89]. Some of the major benefits of antimicrobial medication repurposing include that this method is promising for cancer prevention due to its preexisting safety profile, decreased cost, ability to target common pathways, potential for combating

drug resistance, capability to address medication shortages, synergistic effects with anticancer treatments, and dual mechanistic actions [16] (Figure 5). Drug repurposing is a promising technique for advancing drug development due to its numerous benefits [90]. Repurposing medications with known safety profiles, such as FDA-approved antibiotics, offers a significant advantage [91]. This minimises the need for thorough safety evaluations, leading to faster drug development [92]. As a result, drug discovery costs are reduced, making this strategy more economically feasible [93]. Repurposed antibiotics can target shared pathways in bacterial infections and cancer, making them a viable tool [16]. Antibiotics like rifampicin can block DNA and protein synthesis by targeting bacterial DNA-dependent RNA polymerase [94]. By binding to this enzyme, it can block RNA synthesis (transcription), which inhibits protein synthesis and leads to bacterial death [95]. The similarity shows that existing drugs can be reused to treat cancer. Synergistic behaviour improves antibiotic efficacy in treating cancer [96]. Combining azithromycin with chemotherapeutic agents can enhance antitumor activity [97]. These combinations present new opportunities for cancer prevention and treatment [98]. Repurposing relies on a dual mechanism system, such as a medication intended for a specific bacterial target. This bacterium may cause oncogenesis, similar to Salmonella typhi [16]. During repurposing, this medication targets novel targets in the same species to combat bacteria-induced oncogenesis [99]. This allows the medicine to target both previously known and new targets. Pre-existing medications will find new therapeutic applications to address medicinal shortages [100]. These properties support drug discovery and clinical trials [101]. Medication repurposing is a crucial approach for medication discovery [102]. This also provides new treatment options for pre-existing medication resistance [103]. Drug repurposing is necessary because of the poor discovery rate of drugs in comparison to the progression [104]. Drug repurposing is a successful technique for drug development, as there is only one choice for controlling chronic conditions, utilising existing medications [105]. Antibiotic repurposing has been demonstrated to have anticancer effects, as mentioned in the sections below. [16]

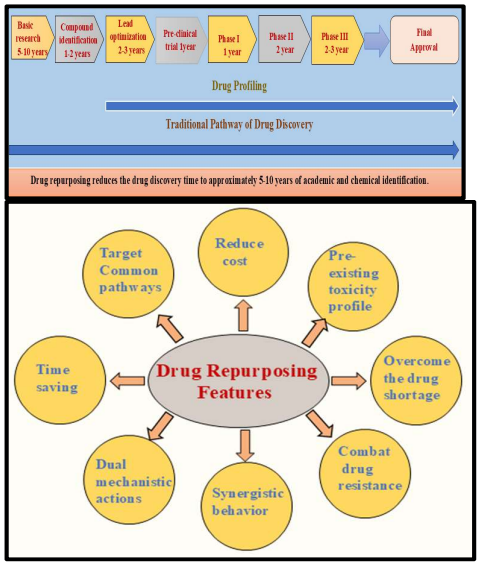

Fig 5. Drug repurposing can decrease drug discovery timelines by utilizing pre-existing toxicity profiles, reducing costs, targeting common pathways, combating resistance, saving time, dual mechanistic action, synergistic behaviors, and addressing drug shortages.

6. Mechanistic Role of Antibiotics in Combating Cancer

Antibiotics give strong action in combating bacterial infections, because of their target mechanism [106]. So, they can be used to treat cancer caused by these bacteria. Cancer involves a variety of mechanisms, including persistent inflammation, cytokine production (e.g., IL-6 and TNF-α), altered cell signalling, and DNA damage. Bacteria cause infection at specific sites, such as the gallbladder, small intestine, liver and lungs, where bacteria can produce toxins that cause inflammation at the injection site [16]. Cellular processes were disrupted, and Cytokines were released. JAK-STAT and MAPK (Mitogen-Activated Protein Kinase) are signalling pathways that are modulated through phosphorylation, which triggers many cancer-related processes, especially uncontrolled cell growth (proliferation), new blood vessel formation (angiogenesis) decrease cell death (apoptosis) and Autophagy, which is a cellular self-cleaning mechanism [107]. Most of the antibiotics target these to treat cancer. For example, minocycline, which belongs to the tetracycline class of antibiotics, binds with IL-6 (interleukin-6) and TNF-α (tumour necrosis factor-alpha), which are mainly released by macrophages, T-cells, immune cells and lymphocytes during infection, inflammation and tissue damage, inhibiting tumour signalling pathways and promoting apoptosis in cancer cells [108]. In addition, drugs like ciprofloxacin

belong to the fluoroquinolone class of antibiotics blocks the excessive production of efflux pump proteins [109]. In the same way, certain antibiotics induce bacterial death, whereas some antibiotics regulate toxin production through direct interaction with their bacterial targets. As a result, inflammation is regulated and decreases cancer formation [110]. The exact mechanism of cancer prevention is still unknown, but it is effective in the prophylaxis of cancer. For this reason, researchers are interested in exploring new possibilities and focusing on obstacles in drug discovery [111].

7. Current Experimental Evidence Supporting Antibiotics as Anticancer Agents

The main function of antibiotic drugs is antibacterial activity, but research shows they also possess anticancer properties [112,113]. Several antibacterial agents show activity against molecular targets that are linked to cancer development. Ribosomal S6 kinase 4 (RSK4) is a protein kinase involved in intracellular signalling and regulation of cell growth are the main target in colon and lung cancers, according to research [16]. RSK4 controls essential cellular functions that include both cell growth and cell movement [114,115]. One of the studies shows that the RSK4 reduces the tumour growth and propagation in mice compared with RSK4+ cancer cells [116,117]. Trovafloxacin demonstrated anticancer properties through its ability to inhibit RSK4 expression while activating caspases and decreasing anti-apoptotic protein levels, including Bcl-2. Doxycycline functions as a cancer prevention agent because it blocks integrin αvβ3, which scientists consider a potential cancer treatment target due to its role in cancer cell growth and movement [16]. Doxycycline blocks the production of vital cell-cycle drivers, which include cyclin D1 and cellular myelocytomatosis oncogene (c-Myc), because these proteins function as essential components for tumour cell growth [118]. Doxycycline shows potential as a cancer treatment because it targets pathways that depend on integrin αvβ3 for cancer progression [119]. The study discovered that azithromycin prevents cancer development by its ability to stop autophagy through its interaction with keratin-18, which leads to the protein's functional disruption [120,121]. The drug shows potential to kill tumour cells because it causes their growth to stop [122,123]. Mitomycin functions as an anticancer drug because it decreases cancer cell proliferation, and doctors currently use it for chemotherapy to treat and prevent cancer [124]. Research has shown that β-lactam antibiotics protect against gastric cancer while also stopping Helicobacter pylori infections [125]. Anthracycline antibiotics display powerful anticancer effects, which make them effective against cancer. The research results demonstrate that repurposing antibiotic medications can create new pathways for developing effective cancer treatment methods [16]. (Table 3)

Table 3. Current Experimental Evidence Supporting Antibiotics as Anticancer Agents

S. no	Antibiotic agent	Anticancer activity	Mehcanism	References
1.	Trovafloxacin	Cytotoxic	Inhibition of p90 ribosomal S_6 kinase 4(RSK$_4$)	[126]
2.	Doxycycline	Antiproliferative	Suppression of cyclin D1 and c-Myc	[127]
3.	Mitomycin	Growth inhibition	Cancer cell proliferation blockade	[128]
4.	Anthracycline	DNA damage	Intercalation into DNA strands	[129]

Conclusion: Antibiotics such as trovafloxacin, doxycycline, mitomycin, and anthracyclines work against cancer by inhibiting RSK4, suppressing cyclin, inhibiting proliferation, and intercalating the DNA. Repurposing offers dual-action against bacterial infections and cancer, cutting costs by 70%, permitting speedier trials, and overcoming resistance via synergies—positioning it as a potential option for difficult malignancies.

CRediT author statement

Pooja kumari: Writing the paper, Data curation and Data Analysis or Investigation; **Salahuddin:** Conceptualisation; **Avijit Mazumder:**

Visualisation; **Rajnish Kumar:** Methodology

Ethical approval and consent to participate

Not Applicable

Human and animal rights

Not Applicable

Consent for publication

Not applicable. The study does not contain data from any person.

Availability of data and materials

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