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Cancer Drug Repurposing: Pathophysiology, Therapeutic Targeting and Translational Opportunities

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ABSTRACT

Cancer remains a major global health challenge because of biological heterogeneity, genomic and epigenomic instability, metastatic dissemination, and the emergence of therapeutic resistance. The global burden has continued to increase, with the International Agency for Research on Cancer (IARC) estimating approximately 20.0 million new cancer cases and 9.7 million cancer deaths worldwide in 2022. Conventional drug discovery is lengthy and costly and is associated with substantial attrition during development. Drug repurposing—the investigation of an established medicine for a new therapeutic indication—can exploit existing pharmacological, toxicological, manufacturing, and clinical information while still requiring disease-specific efficacy and safety evaluation. This narrative review integrates current concepts in cancer pathophysiology, tumor heterogeneity, cancer stem cells, the tumor microenvironment, invasion and metastasis, therapeutic resistance, and mechanism-based treatment with opportunities for pharmacological repurposing. Non-oncology medicines investigated for anticancer indications, including metformin, celecoxib, mesalamine, quinacrine, levofloxacin, and ketoconazole, are distinguished from established anticancer agents evaluated through reformulation, alternative delivery, or combination technologies. The review also examines selected psychiatric medicines and radiotherapy-associated strategies. Evidence is explicitly categorized according to study type and translational maturity. Overall, drug repurposing is a complementary strategy rather than a substitute for conventional drug discovery; its clinical value depends on mechanistic validation, clinically achievable exposure, biomarker-guided selection, dose optimization, controlled trials, and careful assessment of toxicity and drug–drug interactions.

KEYWORDS: Cancer; Drug Repurposing; Drug Repositioning; Tumor Heterogeneity; Cancer Stem Cells; Tumor Microenvironment; Therapeutic Targeting; Metastasis; Therapeutic Resistance; Precision Oncology

1. INTRODUCTION

Cancer is a heterogeneous group of diseases characterized by abnormal cellular proliferation, impaired regulation of cell death, genomic and epigenomic alterations, tissue invasion, and metastatic dissemination. IARC estimates indicate that approximately 20.0 million new cancer cases and 9.7 million cancer deaths occurred worldwide in 2022, including non-melanoma skin cancers [1-2]. Lung cancer was the most frequently diagnosed cancer globally, followed by female breast and colorectal cancers [3-4]. These data emphasize the continuing need for effective, accessible, and biologically informed therapeutic strategies.

Drug repurposing, or drug repositioning, involves investigating an existing medicine for a new therapeutic indication. In oncology, this strategy can exploit prior information on pharmacology, human exposure, formulation, manufacturing, safety, and adverse effects, but those advantages do not establish efficacy for the new indication [5–7]. The dose, schedule, treatment duration, combination partners, and disease context may differ from the original use and can therefore alter both benefit and risk [5,6].

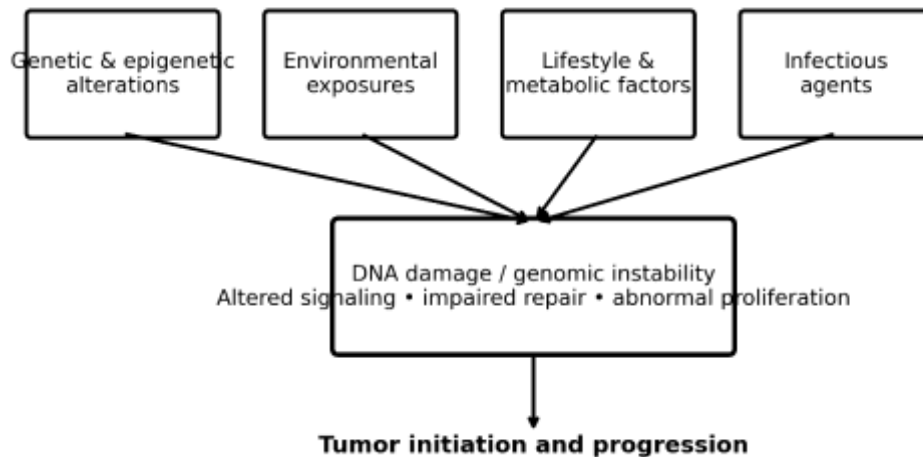
1.1. Literature identification and selection methodology

Literature for this narrative review was identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, supplemented by authoritative cancer-agency resources and reference-list screening. The search covered publications available through September 2026, with emphasis on recent literature for cancer epidemiology, tumor biology, therapeutic resistance, drug repurposing, and clinical translation and on primary studies for individual drug candidates. Principal search concepts combined “cancer drug repurposing,” “drug repositioning,” “tumor heterogeneity,” “cancer stem cells,” “tumor microenvironment,” “therapeutic resistance,” and individual drug names with “cancer,” “anticancer,” “mechanism,” “clinical trial,” “nanoparticle,” or “radiotherapy.” Studies were selected when they directly addressed the biological mechanism, anticancer activity, clinical association, formulation/delivery strategy, or translational limitation discussed in the review. Priority was given to peer-reviewed primary studies, systematic reviews/meta-analyses, major narrative reviews, and authoritative epidemiological reports. Evidence was classified as observational, in vitro, animal/preclinical, clinical-trial, or established clinical use. Claims without a directly verifiable supporting source were removed or rewritten.

2. ETIOLOGY AND PATHOPHYSIOLOGY OF CANCER

Cancer develops through the progressive accumulation and selection of molecular and cellular alterations that disrupt mechanisms controlling proliferation, differentiation, DNA repair, senescence, apoptosis, and tissue organization. Genomic alterations include point mutations, insertions and deletions, copy-number changes, chromosomal rearrangements, and other structural abnormalities; epigenetic remodeling can alter gene expression without changing the DNA sequence. These alterations interact with altered signaling, metabolism, immune surveillance, and tissue architecture to produce an evolving malignant phenotype [7,8]. The etiology of cancer is multifactorial. Genetic susceptibility interacts with environmental exposures, lifestyle factors, chronic inflammation, metabolic abnormalities, and infectious agents, and the relative contribution varies among cancer types and populations. Carcinogenic exposure does not inevitably result in malignancy because dose, duration, tissue susceptibility, DNA repair, immune surveillance, and the accumulation of additional alterations influence progression [9,10].

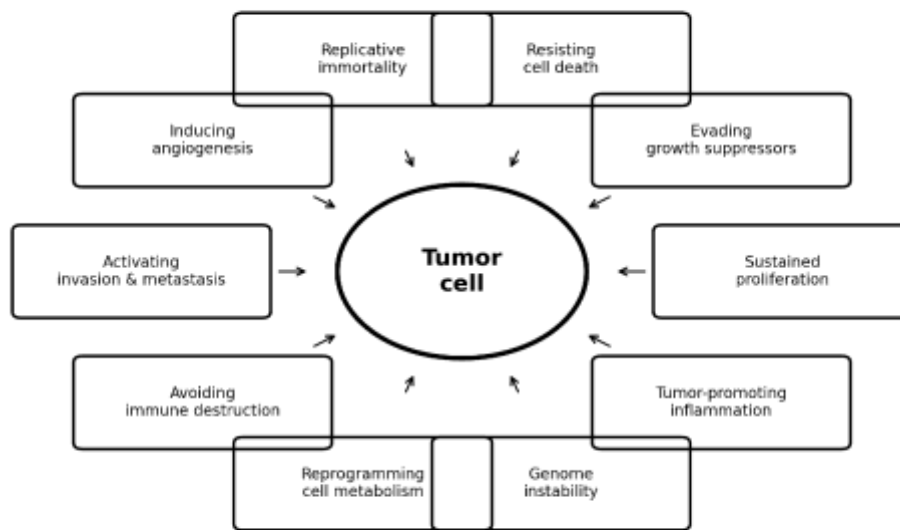
Multifactorial Etiology of Cancer



3. SIGNIFICANCE OF CANCER THERAPY AND THERAPEUTIC RESPONSE

The biological complexity of cancer has direct implications for treatment. A tumor contains malignant cells together with immune cells, fibroblasts, endothelial cells, extracellular matrix, blood vessels, and signaling molecules. Cellular populations within the same tumor can differ in proliferation, differentiation, metabolism, immune interaction, drug sensitivity, and metastatic capacity. Mechanism-based therapies therefore target defined dependencies, including oncogenic signaling, DNA repair, angiogenesis, hormone signaling, apoptosis, metabolism, and immune regulation [2,3]. Surgery, radiotherapy, cytotoxic chemotherapy, targeted therapy, and immunotherapy remain complementary components of cancer management. Resistance may be intrinsic or acquired. Tumor cells can activate bypass pathways, acquire secondary alterations, change epigenetic or metabolic states, alter drug transport, or receive protective signals from the microenvironment. Intratumoral heterogeneity allows resistant subpopulations to survive treatment and expand, while stromal and immune components can modify drug penetration and survival signaling [3,4]. Rational combination therapy and biomarker-guided treatment can address selected resistance mechanisms, although combined toxicity and treatment complexity remain important constraints.

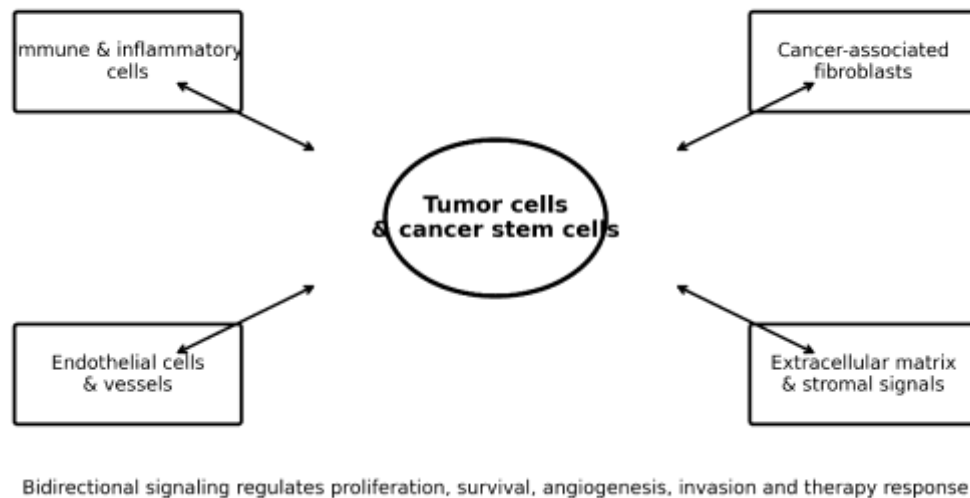
Core Hallmarks of Cancer



4. CANCER CELLS, CANCER STEM CELLS AND TUMOR HETEROGENEITY

Tumor heterogeneity occurs between patients, between primary and metastatic lesions, and among cell populations within a single tumor. It reflects genetic evolution, epigenetic remodeling, environmental selection, and interactions with the tumor microenvironment [11]. Cancer stem-cell (CSC) populations have been associated with self-renewal, tumor initiation, phenotypic plasticity, recurrence, metastasis, and therapeutic resistance, although CSC phenotypes and functional importance vary across tumor types and experimental systems [20]. The tumor microenvironment is composed of fibroblasts, endothelial cells, immune cells, extracellular matrix, and soluble mediators that interact bidirectionally with malignant cells. These interactions can support tumor growth, invasion, angiogenesis, immune modulation, and therapeutic resistance [12-13]. Consequently, the biological context in which a drug acts can influence both efficacy and resistance, providing a rationale for investigating agents that modulate inflammatory, metabolic, stromal, or survival pathways as components of combination strategies.

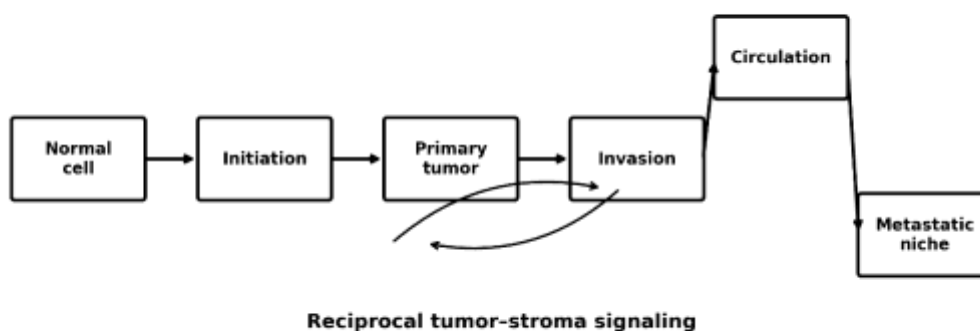
Tumor Microenvironment and Cancer Stem-Cell Interactions



5. TUMOR MICROENVIRONMENT, INVASION AND METASTASIS

Metastasis is a multistep process involving local invasion, intravasation, survival in the circulation, extravasation, adaptation to a distant tissue, and establishment of secondary disease. Successful dissemination depends on both tumor-cell properties and the permissiveness of the target tissue. Interactions between malignant cells and stromal components can influence proliferation, invasion, angiogenesis, inflammation, and metastatic colonization [4]. Hypoxia, abnormal vascular perfusion, extracellular-matrix barriers, inflammatory signaling, and protective paracrine factors can reduce drug exposure or activate survival pathways within tumors [4]. These features support therapeutic approaches that combine tumor-cell targeting with modulation of relevant microenvironmental dependencies, provided that the mechanism is experimentally validated and the therapeutic window is acceptable.

Tumor Progression, Stromal Signaling and Metastatic Dissemination

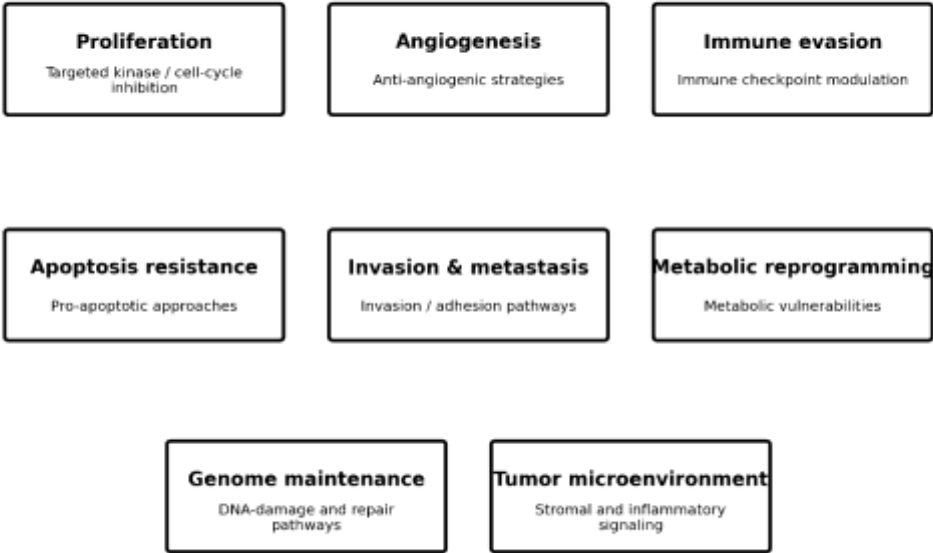


6. THERAPEUTIC TARGETING AND THE HALLMARKS OF CANCER

Therapeutic targeting exploits biological dependencies that distinguish malignant from normal tissue. Current strategies include inhibition of growth-factor receptors and intracellular kinases, angiogenic signaling, DNA-repair pathways, hormone signaling, apoptosis-regulating proteins, metabolic pathways, and immune checkpoints [2,3]. The relevant endpoint is not targeting inhibition alone but whether modulation of the target produces reproducible antitumor activity in the disease context. Because tumors can use parallel signaling routes and adapt under treatment pressure, inhibition of a single pathway may be bypassed by pathway redundancy or acquired resistance [3]. Biomarkers that identify pathway dependence and predict response can improve patient selection. Combination approaches may be useful when they address complementary vulnerabilities, but their development requires evidence that the combination provides sufficient biological or clinical benefit to justify additional toxicity and complexity. The hallmarks framework provides a conceptual basis for linking malignant phenotypes with therapeutic strategies. Sustained proliferative signaling, resistance to cell death, angiogenesis, immune evasion, altered metabolism, invasion, and metastatic behavior can each be associated with distinct therapeutic targets, while genomic instability and tumor-promoting inflammation can influence several hallmarks simultaneously [2].

Therapeutic Targeting of Cancer Hallmarks

Precision therapy aims to disrupt tumor-specific dependencies while limiting damage to normal tissue



7. DRUG REPURPOSING AS A STRATEGY FOR CANCER THERAPEUTICS

7.1 Non-oncology medicines investigated for new anticancer indications

Drug repurposing starts with a medicine developed or established for one indication and investigates a new therapeutic use. In oncology, this may include non-oncology medicines with established human exposure and pharmacology. Evidence from observational studies,

cell systems, animal models, and clinical trials should be interpreted according to the level of evidence and the exposure achievable in humans [5–7].

Metformin: Metformin, an established antidiabetic medicine, has been associated with a lower incidence of colorectal cancer in several observational studies and meta-analyses. A 2020 meta-analysis of 17 studies involving more than one million patients with diabetes reported a lower colorectal-cancer incidence among metformin users, although heterogeneity and the observational nature of much of the evidence limit causal interpretation [8]. Experimental effects on energy metabolism and growth signaling provide mechanistic rationale for further investigation, but metformin is not an established anticancer treatment.

Celecoxib: Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor investigated for colorectal chemoprevention, particularly in familial adenomatous polyposis (FAP). A randomized placebo-controlled trial reported reductions in colorectal polyp burden after six months of celecoxib treatment [9]. These findings concern chemoprevention rather than treatment of established metastatic cancer, and cardiovascular, renal, and gastrointestinal safety remain important considerations.

Mesalamine: Mesalamine (5-aminosalicylic acid), established for inflammatory bowel disease, has been investigated for colorectal cancer chemoprevention and cellular effects. Clinical and experimental studies report increased apoptosis and reduced proliferation in colorectal mucosa or colon carcinoma cells, including caspase-dependent apoptosis and mitotic arrest [10,11]. These findings provide a biological rationale for investigation but do not establish mesalamine as an anticancer therapy.

Quinacrine: Quinacrine, an established antimalarial/antiprotozoal medicine, has been investigated as an experimental anticancer agent. In ovarian-cancer models, quinacrine promoted autophagy-dependent cell death, increased chemosensitivity, reduced p62/SQSTM1, and suppressed tumor growth in vivo, including in a chemoresistant model [12]. The evidence remains preclinical and requires clinically relevant exposure and controlled clinical evaluation.

Levofloxacin: Levofloxacin, an established fluoroquinolone antibiotic, has been investigated for anticancer activity. Experimental studies reported inhibition of breast-cancer proliferation and induction of apoptosis through effects on mitochondrial biogenesis [13], while lung-cancer models showed mitochondrial dysfunction, oxidative stress, reduced ATP production, and tumor-growth inhibition [14]. These findings are preclinical and do not support routine anticancer use.

Ketoconazole: Ketoconazole, an antifungal agent that inhibits steroidogenic cytochrome P450 enzymes, has been investigated in prostate cancer because androgen synthesis can persist despite androgen-deprivation therapy. Clinical studies evaluated ketoconazole-containing regimens in androgen-independent or castration-resistant prostate cancer and reported antitumor or prostate-specific-antigen responses [15]. Its use is limited by toxicity, drug interactions, and the availability of more selective androgen-synthesis inhibitors.

Acetaminophen: Acetaminophen should not be classified as an anticancer repurposing candidate on the basis of epidemiological risk observations. A systematic review and meta-analysis of seven observational studies found no overall association between acetaminophen use and endometrial-cancer risk [16]. This evidence is relevant to epidemiology rather than therapeutic efficacy and is therefore excluded from the repurposing evidence table.

7.2 Established anticancer medicines: reformulation, alternative delivery and combination strategies

5-Fluorouracil (5-FU): 5-FU is an established anticancer drug; therefore, nanoparticle-based delivery represents reformulation/alternative drug delivery rather than classical repurposing. Recent work has evaluated chitosan-based nanoparticles, including targeted formulations, to improve 5-FU localization and delivery in colorectal cancer models [17].

Doxorubicin: Doxorubicin is an established anthracycline anticancer drug. Nanocarrier systems that co-deliver doxorubicin with siRNA represent formulation and combination strategies intended to improve tumor delivery and overcome resistance. Experimental studies have reported enhanced delivery and antitumor activity with co-delivery systems [18].

Paclitaxel: Paclitaxel is also an established anticancer medicine. Nanostructured lipid carriers have been investigated for pulmonary co-delivery of paclitaxel or doxorubicin with siRNAs directed against resistance-associated targets in lung-cancer models [19]. This is an alternative delivery and combination approach, not repurposing of a non-oncology medicine.

Epirubicin: Epirubicin is an established anthracycline. Its activity is linked to topoisomerase II targeting, and tumor topoisomerase II α expression has been investigated as a predictor of response to epirubicin-containing chemotherapy in breast cancer [20]. Studies of liposomal or other delivery systems for epirubicin should therefore be described as reformulation or drug-delivery optimization rather than indication repurposing.

Taken together, the evidence separates genuine indication repurposing from formulation science. Metformin, celecoxib, mesalamine, quinacrine, levofloxacin, and ketoconazole represent non-oncology medicines investigated for cancer-related applications, whereas 5-FU, doxorubicin, paclitaxel, and epirubicin are established anticancer drugs being evaluated through delivery, formulation, or combination strategies.

Table-1 Evidence matrix for principal drug candidates

Candidate	Established indication	Anticancer application	Proposed mechanism	Cancer type	Evidence level	Key limitations	References
Metformin	Type 2 diabetes	Risk/prognostic associations; experimental anticancer investigation	AMPK/metabolic and growth-signaling effects	Colorectal cancer	Observational + preclinical	Confounding, heterogeneity; randomized efficacy not established	[8]
Celecoxib	Pain/inflammation; FAP chemoprevention context	Colorectal adenoma chemoprevention	COX-2/prostaglandin pathway inhibition	FAP/colorectal polyps	Clinical trial	Cardiovascular, renal and GI risks; prevention $\neq$ treatment	[9]
Mesalamine	Inflammatory bowel disease	Colorectal chemoprevention /cell-growth modulation	Reduced proliferation; caspase-dependent apoptosis	Colorectal mucosa /carcinoma	Clinical + in vitro	Limited clinical oncology endpoints	[10,11]

Quinacrine	Antimalarial/antiprotozoal	Experimental treatment/chemo sensitization	Autophagy, p62/SQSTM1, apoptotic signaling	Ovarian cancer	In vitro + animal	Human exposure and efficacy not established	[12]
Levofloxacin	Bacterial infections	Experimental anticancer activity	Mitochondrial dysfunction, oxidative stress	Breast and lung cancer	In vitro + animal	Preclinical; antibiotic safety/exposure constraints	[13,14]
Ketoconazole	Fungal infections	Androgen-synthesis inhibition in prostate cancer	CYP-mediated steroidogenesis inhibition	Castration-resistant/androgen-independent prostate cancer	Clinical studies	Drug interactions, hepatotoxicity and less selective endocrine options	[15]
Acetaminophen	Analgesic/antipyretic	Not supported as anticancer therapy; epidemiological risk question only	No therapeutic anticancer mechanism established	Endometrial cancer risk	Observational meta-analysis	Null epidemiological association does not support repurposing	[16]
5-Fluorouracil	Established anticancer chemotherapy	Nanoparticle/targeted delivery	Controlled or localized drug release	Colorectal cancer	Preclinical/formulation research	Already an oncology drug; delivery benefit requires clinical validation	[17]
Doxorubicin	Established anthracycline chemotherapy	Nanocarrier co-delivery with siRNA	Tumor delivery plus resistance-gene silencing	Multiple experimental tumors	Preclinical	Formulation complexity, toxicity and translation	[18]
Paclitaxel	Established anticancer chemotherapy	Nanostructured lipid carrier and siRNA co-delivery	Targeted pulmonary delivery and resistance modulation	Lung cancer	Preclinical	Formulation/PK and clinical validation required	[19]
Epirubicin	Established anthracycline chemotherapy	Formulation optimization; biomarker-guided use	Topoisomerase II targeting	Breast cancer	Clinical chemotherapy + biomarker evidence	Not repurposing; anthracycline toxicity	[20]

8. ANTINEOPLASTIC POTENTIAL OF PSYCHIATRIC MEDICINES

Psychiatric medicines have attracted interest as potential anticancer candidates because some exhibit effects on epigenetic regulation, mitochondrial function, apoptosis, autophagy, dopamine signaling, serotonin-related pathways, or chromatin-modifying enzymes. The available evidence is predominantly preclinical, and the concentrations used in vitro may not correspond to clinically achievable exposures. Accordingly, these agents should be considered investigational candidates rather than established cancer treatments [21–28]. Valproic acid is an established antiepileptic and mood-stabilizing medicine with histone-deacetylase-inhibitory activity. Preclinical studies and early clinical investigations have examined its effects on proliferation and its potential to enhance selected anticancer treatments [21]. Phenothiazines such as chlorpromazine and thioridazine have shown antiproliferative, pro-apoptotic, mitochondrial, and cancer-stem-cell effects in experimental models [22,23]. Pimozide has shown inhibition of breast- and lung-cancer cell growth, apoptosis, and antitumor activity in xenograft models [24]. SSRIs, including fluoxetine and sertraline, have produced antiproliferative and apoptotic effects in several experimental cancer systems, although clinical efficacy remains unestablished [25]. Tricyclic antidepressants such as imipramine and amitriptyline have likewise shown apoptosis-inducing and antiproliferative effects in selected tumor models [26,27]. Tranylcypromine is of interest because it can inhibit LSD1/KDM1A, an epigenetic regulator implicated in cancer; a phase I/II study evaluated tranylcypromine with all-trans-retinoic acid in relapsed/refractory acute myeloid leukemia [28]. These observations support hypothesis generation and further translational investigation. The principal barriers are clinically achievable exposure, dose-limiting adverse effects, pharmacodynamic target engagement, drug interactions, and the need to demonstrate benefit in controlled clinical studies.

Table 2. Psychiatric medicines with reported or proposed antineoplastic effects

Drug/class	Primary indication(s)	Primary pharmacological action	Proposed anticancer relevance	Refs.
Valproic acid	Epilepsy; bipolar disorder	HDAC inhibition; ion-channel effects	May alter proliferation, differentiation and apoptosis; may enhance selected anticancer regimens	[21]
Phenothiazines (chlorpromazine; thioridazine)	Psychotic disorders	Dopamine-receptor antagonism	Experimental antiproliferative, pro-apoptotic, mitochondrial and cancer-stem-cell effects	[22,23]
Pimozide	Psychiatric/tic disorders	Dopamine/serotonin receptor antagonism	Inhibits proliferation and promotes apoptosis; signaling effects reported in breast and lung cancer models	[24]
SSRIs (fluoxetine; sertraline)	Depression and related disorders	Serotonin-transporter inhibition	Experimental apoptosis, cell-cycle effects and signaling changes; clinical	[25]

			anticancer efficacy unestablished	
Tricyclic antidepressants (imipramine; amitriptyline)	Depression and related disorders	Monoamine-transporter inhibition	Experimental antiproliferative and apoptosis-inducing effects	[26,27]
MAO/LSD1-directed strategy (tranylcypromine)	Depression	MAO inhibition; LSD1 inhibition at relevant pharmacological contexts	Epigenetic differentiation strategy investigated in AML, including combination with ATRA	[28]

9. RADIO THERAPY AND REPURPOSING STRATEGIES

Radiotherapy remains an important component of cancer treatment and is frequently combined with surgery or systemic therapy. Ionizing radiation kills tumor cells largely through DNA damage, including double-strand breaks, while cellular response depends on DNA-damage sensing and repair, cell-cycle state, oxygenation, and the tumor microenvironment [29,30].

Repurposed medicines may be investigated as radiosensitizers when they modulate DNA repair, hypoxia responses, metabolism, angiogenesis, proliferation, or survival signaling. Targeting DNA-damage-response pathways can increase tumor radiosensitivity, but the therapeutic objective is to increase tumor control without producing unacceptable normal-tissue toxicity [29,30].

Contemporary radiotherapy uses image guidance and highly conformal techniques, including intensity-modulated, stereotactic, and proton-based approaches in selected clinical settings. Biological heterogeneity remains relevant even with precise dose delivery, supporting investigation of molecularly informed radiosensitization and combinations [29].

10. CHALLENGES AND FUTURE PERSPECTIVES

Despite its potential, cancer drug repurposing faces several translational challenges. Mechanistic observations may not translate from cell culture or animal models to patients, and concentrations required for experimental activity may exceed clinically achievable exposure. Dose, schedule, combination partners, disease stage, genomic background, and microenvironment can alter the pharmacological effect and safety profile [5–7]. A stronger repurposing pipeline should integrate computational hypothesis generation with experimental validation and clinical biomarker development. Drug–target, transcriptomic, proteomic, metabolic, and real-world clinical datasets can help identify candidate medicines and patient populations. These hypotheses should then be tested through target-engagement studies, disease-relevant models, pharmacokinetic/pharmacodynamic analysis, and appropriately designed clinical trials [5,7]. Rational combinations may be particularly useful when a repurposed medicine addresses a defined resistance mechanism or complements an established therapy. Examples include modulation of inflammatory signaling, tumor metabolism, angiogenesis, DNA repair, or the tumor microenvironment. Such combinations require a mechanistic rationale, biomarker strategy, dose optimization, and prospective evaluation rather than empirical addition of multiple agents. Evidence should be interpreted

according to clinical maturity. An established indication, an observational association, an in vitro effect, an animal response, and a controlled clinical trial represent different levels of evidence and should not be treated as interchangeable. Repurposing claims therefore require explicit reporting of evidence level, clinically relevant exposure, toxicity, interactions, and study limitations.

11. CONCLUSION

Cancer is a biologically complex and continuously evolving disease in which genomic instability, tumor heterogeneity, cancer stem-cell populations, microenvironmental signaling, invasion, metastasis, and therapeutic resistance interact to shape treatment response [1–4]. Conventional anticancer drug development remains resource-intensive, whereas drug repurposing can leverage existing pharmacological and clinical information to investigate new indications [5–7]. The evidence reviewed here supports a clear distinction between genuine indication repurposing of non-oncology medicines and reformulation, alternative delivery, or combination strategies involving established anticancer drugs. Metformin, celecoxib, mesalamine, quinacrine, levofloxacin, and ketoconazole illustrate different stages of investigation of non-oncology medicines, while 5-FU, doxorubicin, paclitaxel, and epirubicin are better categorized under delivery or formulation optimization. Psychiatric medicines and radiotherapy-associated strategies provide additional investigational avenues. Translation to oncology practice will require reproducible mechanisms, clinically achievable exposure, biomarker-guided patient selection, optimized dosing, careful assessment of interactions and toxicity, and well-controlled clinical trials.

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