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Therapeutic Potential of Aspirin Repurposing in Colon Cancer

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ABSTRACT

Repurposing existing drugs for new therapeutic applications offers significant advantages over conventional drug development. Since these drugs have already passed safety evaluations, their failure rate is significantly reduced. In addition, leveraging pre-existing clinical data and established manufacturing methods accelerates the development process and reduces costs. While bringing a new drug to market typically requires 10-17 years and $2-3 billion, repurposed drugs can become available in 3-12 years at an estimated cost of $300 million. Colon cancer treatment remains a challenge due to the lengthy and costly nature of traditional drug discovery. This review highlights drug repurposing as a viable alternative to address these obstacles. Various computational and network-driven strategies are examined, including network models (establishing relationships between drugs and diseases); computer-aided techniques (predicting drug-target interactions); machine learning algorithms (identifying hidden patterns in large datasets); and molecular docking simulations (analyzing how drugs bind to specific molecular targets). Aspirin has emerged as a promising candidate for repurposing in the treatment of colon cancer due to its potential to inhibit cancer cell proliferation. Furthermore, this review highlights the growing role of artificial intelligence and network modeling in advancing drug repurposing efforts. By utilizing state-of-the-art computational tools and personalized medicine approaches, repurposing existing drugs offers an efficient and cost-effective strategy for improving colon cancer treatment options.

Keywords: Colon cancer, Drug repurposing, Aspirin, Molecular docking, Network modeling

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Introduction

Drug repurposing, also known as therapeutic switching or repositioning, involves identifying new therapeutic applications for existing drugs. This includes old medications, that failed in previous trials, experimental, FDA-approved, or pro-drugs. The process extends beyond the original intended use of a drug, uncovering its hidden therapeutic potential [1].

This approach presents several advantages over developing entirely new drugs, as illustrated in **Figure 1**. First, since repurposed drugs have already undergone safety evaluations in preclinical studies and, in some cases, early human trials, the likelihood of failure—especially due to safety concerns—is significantly lower. Second, because many preclinical tests, safety assessments, and formulation developments have already been completed, the

overall development timeline can be shortened. Third, investment requirements may be lower, though this depends on the drug's stage in the development process. While phase III trials and regulatory approval costs may still be substantial, expenses associated with preclinical, phase I, and phase II trials are considerably reduced [2].
These advantages contribute to a lower overall cost when accounting for potential failures, making repurposed drug development a less risky investment with a faster return. On average, bringing a repurposed drug to market costs around $300 million, whereas developing a new chemical entity can range from $2 to $3 billion. Additionally, repurposed drugs may lead to the discovery of new therapeutic targets and areas of research [2]. Studies suggest that developing and approving a novel drug typically takes 10 to 17 years, whereas repurposed drugs can reach the market within 3 to 12 years at nearly half the cost of newly developed drugs [3].

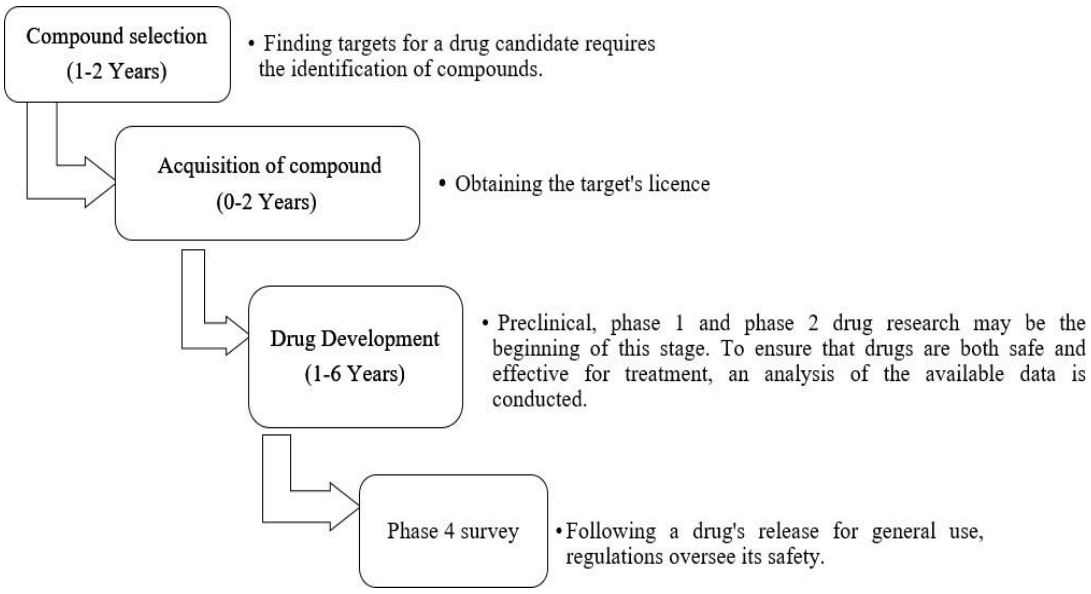

Figure 1. Four stages of drug repurposing: 1) compound selection, 2) acquisition of compound, 3) drug development, and 4) phase 4 survey

Cancer remains a major global health challenge, with significant unmet medical needs despite substantial advancements in treatment strategies. Scientists continue to explore innovative therapeutic approaches to combat this complex disease [4]. One promising strategy is drug repurposing, which involves finding new therapeutic applications for already-approved drugs. This approach is gaining increasing attention from both academic researchers and the pharmaceutical industry as a potential method to accelerate cancer treatment development [5].
Colon cancer is the second leading cause of cancer-related deaths in the United States. The American Cancer Society compiles and updates colorectal cancer (CRC) statistics every three years using data from population-based cancer registries and the National Center for Health Statistics. Projections for 2023 estimate approximately 153,020 new CRC cases and 52,550 deaths. Among these, 19,550 diagnoses and 3,750 deaths are expected in individuals under 50 years old [6].
Traditional colon cancer treatments include surgery and chemotherapy, which have long been the primary treatment options. Other emerging therapies include gene therapy, immunotherapy, adoptive T-cell therapy, complement inhibition, cytokine therapy, and natural product-based treatments [7].
While monitoring colorectal metastases has remained largely unchanged over the past decade, advances in systemic and liver-directed therapies are improving survival rates. Additionally, innovative image- and pathology-guided treatments are reshaping rectal cancer management [8]. Emerging data suggest that non-surgical approaches may offer comparable long-term outcomes for select patients, potentially reducing the need for radical surgery, except in cases of local recurrence after neoadjuvant therapy. Precise monitoring techniques are crucial to guiding treatment decisions, particularly for stage IV colon cancer patients, ensuring optimal therapeutic outcomes [8].
The treatment of colon cancer remains a challenge due to the lengthy and costly nature of traditional drug discovery. This review highlights drug repurposing as a viable alternative to address these obstacles.

Results and Discussion

The need for drug repurposing

Drug repurposing holds immense potential for addressing unmet medical needs in rare, orphan, and neglected diseases. By leveraging existing scientific knowledge and pharmaceutical resources, this approach can accelerate therapy development and improve patient outcomes [9].

Repurposing already-approved drugs can help overcome the limitations of conventional drug pipelines, leading to more accessible treatments, alternative therapeutic options, and drugs with better safety profiles [10]. The challenges in new drug development include rising research and development (R&D) costs, lengthy approval timelines, low success rates, and regulatory hurdles [11]. Additionally, the pharmaceutical industry faces competition from generic and off-label drugs and financial losses due to patent expirations. From an industry perspective, drug repurposing is seen as a cost-effective, time-efficient, and lower-risk alternative with a higher likelihood of success compared to de novo drug development [12].

Drug repurposing strategies

Computational approach

Various databases and computational tools, such as Drug Predict, DrugBank, Promiscuous, Mantra2.0, PharmDB, DRAR-CPI, repoDB, RepurposeDB, DeSigN, CMap, and DPDR-CPI, are instrumental in drug repurposing efforts [13]. Given the increasing availability of large-scale biomedical data, advanced computational techniques—such as data mining, machine learning, and network analysis—are essential for producing reliable outcomes. These techniques facilitate systematic drug repositioning, identification of new therapeutic potentials, and exploration of alternative applications for approved medications, particularly for complex diseases like cancer [14].

Machine learning

Machine learning models leverage diverse datasets to identify drug repositioning opportunities and predict new drug-disease associations by analyzing underlying biological mechanisms. In recent years, numerous machine-learning methods have emerged, particularly those incorporating multiple data features to improve accuracy [15].

- Menden *et al*. [16] developed models that predict cancer cell line responses to drug treatments based on IC50 values. Their approach utilized chemical properties (e.g., structural fingerprints) and genomic features (e.g., oncogene mutations and microsatellite status) to create a feed-forward perceptron neural network model and a random forest regression model. The predictions underwent cross-validation and independent blind testing for accuracy.
- Napolitano *et al*. [17] took a drug-centric approach to predict drug therapeutic classes, constructing a drug similarity matrix based on chemical structure, molecular targets, and gene expression data. This matrix was then used as a kernel for SVM classification.
- Gottlieb *et al*. [18] expanded on this approach by integrating genetic and phenotypic disorder-related features. They calculated similarity measures between drugs and diseases to generate classification features and applied a logistic regression classifier to predict novel drug applications.
- Collaborative filtering techniques are also used to predict unknown drug-disease relationships. Zhang *et al*. [19] developed a comprehensive computational framework that integrated multiple similarity metrics, including disease phenotypes, drug side effects, genomic features (drug targets and disease genes), and chemical structures. They reformulated drug-disease network analysis as an optimization problem, demonstrating high efficacy in identifying novel therapeutic candidates.
- Yang *et al*. [20] introduced a causal inference-probabilistic matrix factorization (PMF) approach to infer drug-disease relationships. Their model constructed causal networks linking diseases, genes, targets, pathways, and drugs, using known interactions to discover new drug-disease correlations, offering valuable insights for drug repositioning.

Network models

Network-based models use nodes to represent elements like drugs, diseases, or genes, and edges to depict the relationships between them. These networks, built from diverse data sources, visualize interactions such as drug-drug, drug-target, drug-disease, disease-disease, disease-gene, protein-protein, and transcriptional networks [21].

By integrating multiple datasets and applying the "guilt-by-association" principle, network-based approaches can uncover previously unknown relationships between drugs and diseases. This principle suggests that drugs eliciting similar transcriptional responses may have comparable therapeutic effects [22].

- One study compared target-based, drug-based, and network-based models using a bi-partite network to assess their similarity. When evaluated using the area under the receiver operating curve (AUROC), network-based inference was the most effective for predicting drug-target interactions [23].
- Another approach employed a heterogeneous network model to analyze drug-disease interactions by identifying highly interconnected drug-disease modules [24]. This method facilitated the extraction of drug-disease pair data, aiding in the identification of potential candidates for drug repurposing.
- Network modeling has also been applied to cancer drug repurposing by exploring off-target effects on cancer signaling pathways. This approach has helped propose new uses for existing cancer therapies [25].

Molecular docking

Molecular docking plays a crucial role in drug repurposing by predicting interactions between drug molecules and biological targets at the molecular level. This method helps identify potential therapeutic candidates by assessing how well a drug binds to a specific protein target associated with a disease.

During our investigation, we identified a meta-signature of genes capable of distinguishing colon cancer tissues from healthy tissues with high accuracy [26]. Notably, the most significant variables identified through random forest, Glmnet, and edgeR models showed substantial overlap. This overlap suggests that these genes could play a crucial role in colon cancer progression and treatment.

Given these findings, it is imperative to conduct in-silico studies to examine the interactions between the protein products of these genes and various FDA-approved anti-cancer drugs [27]. This approach can reveal new therapeutic potentials for existing drugs, further supporting the drug repurposing strategy.

A few examples of repurposed drugs and their interactions with cancer-related targets are listed in **Table 1**.

Table 1. Notable cases of drug repurposing

Drug name	Original use	New therapeutic use	Repurposing method
Minoxidil	Hypertension	Hair loss	Retrospective clinical analysis
Sildenafil	Angina	Erectile dysfunction	Retrospective clinical analysis
Atomoxetine	Parkinsonism	Attention-deficit hyperactivity disorder (ADHD)	Pharmacological evaluation
Raloxifene	Osteoporosis	Breast cancer	Retrospective clinical analysis
Duloxetine	Pain management (Analgesia)	Premature ejaculation	Pharmacological assessment
Topiramate	Epilepsy	Obesity	Pharmacological evaluation
Ketoconazole	Fungal infections	Cushing's syndrome	Pharmacological assessment
Rituximab	Various cancers	Rheumatoid arthritis	Historical analysis of rheumatoid arthritis remission in lymphoma patients receiving Rituximab
Zidovudine	Cancer	HIV/AIDS	Screening compound libraries in a controlled setting
Thalidomide	Morning sickness	Multiple myeloma	Unapproved use and pharmacological evaluation
Aspirin	Pain relief (Analgesia)	Colon cancer	Retrospective analysis of clinical and pharmacological data

Aspirin and its potential role in cancer treatment

Aspirin (acetylsalicylic acid) as a case of drug repurposing

Aspirin is one of the earliest examples of drug repurposing. Initially developed as a pain reliever, its potential anti-cancer properties have been extensively studied since 1968. Research has demonstrated its effectiveness against various tumor types through both COX-dependent and independent mechanisms [28, 29]. As a non-steroidal anti-inflammatory drug (NSAID), aspirin is being investigated for its role in cancer prevention, particularly colorectal cancer, though the exact mechanisms remain unclear [30, 31].

Based on the results, aspirin hinders the transformation of M1 macrophages into M2 macrophages, thereby enhancing immune response and reducing cancer progression [32]. Furthermore, studies suggest a synergistic effect between aspirin and anti-PD-L1 blockade, which may enhance its anti-tumor efficacy through COX

inhibition [33]. Clinical trials have shown promising results in reducing the risk of colon cancer with aspirin use [34, 35].

Challenges and future directions

Ongoing challenges in cancer treatment

Despite decades of research, cancer remains one of the leading causes of mortality worldwide. The process of developing new cancer therapies often involves repurposing well-known molecular entities originally designed for non-cancerous conditions [36]. Colon cancer, the second deadliest cancer globally, is primarily linked to TP53 gene mutations, which affect the production of the p53 protein [37, 38]. This protein plays a crucial role in eliminating damaged cells through apoptosis or autophagy while supporting the repair of others [39]. Understanding how non-oncology drugs exhibit anticancer activity has been made possible through advancements in genomics and drug screening technologies [40].

Personalized medicine and biomarkers in cancer research

Significant progress has been made in identifying colorectal cancer (CRC) biomarkers, facilitated by innovative techniques such as:

- Organoids and patient-derived xenografts
- Liquid biopsies
- Consensus molecular subtypes (CMS) characterization

To establish a clinically viable gold standard for biomarker development, further validation is required, particularly in quantification, reproducibility, and scalability [41]. Instead of conventional staging-based treatments, cancer therapies are now shifting toward mechanism-based treatments, which focus on the tumor's molecular profile rather than its location or tissue type [42].

While CMS-based classification has advanced treatment personalization, applying this approach in clinical settings remains complex—especially when extracting genome-wide transcriptome data from formalin-fixed, paraffin-embedded tissues. However, recent studies indicate that CMS classification using immunohistochemistry (IHC) with five key markers (CDX2, FRMD6, HTR2B, ZEB1, and KER) can achieve 87% accuracy compared to transcriptome-based classification [43].

Additionally, patient-derived xenografts and tumor organoid technology are emerging as key tools in biomarker discovery. These 3D in vitro tumor models allow researchers to predict patient responses to treatments and optimize personalized therapies [44, 45]. Organoid technology also enables high-throughput screening, aiding in drug repurposing efforts by identifying previously unknown therapeutic applications of existing drugs [46].

Artificial intelligence in colorectal cancer (CRC) diagnosis and treatment

Advances in artificial intelligence (AI), particularly deep learning, are revolutionizing the way colorectal cancer (CRC) is diagnosed and treated. AI tools assist in lesion detection and diagnosis, leading to more personalized treatment plans. These systems help reduce observer bias and distractions, boosting both the speed and accuracy of diagnosis. In some cases, AI can match or even exceed human performance in detecting and diagnosing CRC [47].

AI is also valuable in assessing the quality of screening and diagnostic procedures. For instance, researchers have developed models using natural language processing (NLP) to evaluate colonoscopy quality across various institutions [48]. Additionally, AI-enabled virtual assistants are improving communication between patients and healthcare providers while offering personalized healthcare services. Mobile AI applications, such as the Colour App (Colorectal Cancer Awareness Application), are enhancing public awareness and boosting participation in CRC screening programs [49].

While AI applications offer significant benefits for CRC diagnosis and treatment, challenges remain. Training AI systems to think like humans involve multiple factors, and integrating this technology into clinical workflows remains a significant obstacle. However, with increasing regulatory approvals and support from professional organizations, the use of AI in routine patient care is expected to rise. One of the major hurdles is the high cost of developing AI models, along with challenges in obtaining FDA approval [50].

Privacy concerns also present a challenge. Collaborations between academic research and healthcare companies could potentially expose patient data to privacy breaches. AI-based platforms that analyze data from electronic

medical records (EMRs) or colonoscopy images are being explored, allowing real-time decision assistance and training opportunities. Despite its potential, AI's ability to handle large datasets raises the need for further research to develop appropriate security and privacy protocols for the safe storage and use of medical data [50].

Exploring medication repurposing strategies, particularly through computational methods like machine learning, network modeling, and molecular docking studies, has the potential to revolutionize colon cancer treatment. These computational tools expedite drug discovery by systematically analyzing already-approved medications, offering a cost-effective alternative to more time-consuming approaches. Aspirin, with its proven safety profile and established anti-cancer properties, serves as a prime example of the promising potential of drug repurposing.

However, challenges associated with pharmacological repurposing, such as off-target effects and limited patent protection, must be addressed. These issues highlight the need for more advanced methodologies and regulatory frameworks. Recognizing and addressing these challenges is essential to minimizing risks and ensuring that repurposed drugs can be effectively utilized in colon cancer treatment.

Integrating biomarkers with artificial intelligence (AI) seems crucial to advancing medication repurposing. Biomarkers enable more precise patient categorization, which in turn improves the likelihood of positive treatment outcomes. Additionally, AI, with its ability to analyze large datasets and predict therapeutic efficacy, has the potential to reshape the drug discovery landscape. This discussion emphasizes the promising future of medication repurposing in colon cancer, particularly through computational techniques, with aspirin as a successful case study. By overcoming challenges and incorporating advanced technologies like biomarkers and AI, a more effective, personalized approach to colon cancer therapy can be achieved, improving patient outcomes and bringing us closer to precision medicine.

Conclusion

The exploration of medication repurposing for colon cancer treatment, particularly with aspirin, demonstrates a promising strategy for addressing treatment challenges. Through the integration of computational tools, machine learning, and molecular docking, aspirin has emerged as a strong candidate for repurposing. The future of customized treatments for colon cancer relies heavily on advancements in personalized medicine and the use of artificial intelligence to tailor therapies for individual patients. This review provides a comprehensive overview of repurposing strategies and aims to guide researchers and clinicians toward more effective and targeted interventions. As the field progresses, the ongoing use of aspirin in medication repurposing offers hope for better treatment outcomes in colon cancer, paving the way for more sophisticated, patient-centered, and innovative cancer therapies.

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