A Comprehensive Review on Drug Repurposing in Cancer Treatment

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

Cancer, a complex and highly detrimental group of medical conditions, continues to become a significant global health burden. Despite oncology research's advances, cancer drug development has fallen behind due to a number of factors such as rising failure rates, high costs, low bioavailability, many adverse effects, and a lengthy design and evaluation process. This indicates a large unmet need for better cancer treatments, which has encouraged drug repurposing. Drug repurposing refers to discovering a novel therapeutic application for an approved drug. Drugs belong to different therapeutic classes have shown anticancer potential in several studies. These may destroy cancer cells or influence their behavior in existing tumors. This study reviews various non-cancer drug categories that have shown promise in preclinical and clinical trials for repurposing them in cancer treatment, along with their mechanisms of action and the suitability for certain malignancies.

Keywords: Cancer; Antibiotics; Antidiabetics; NSAIDs; Antiviral; Drug repurposing

Dedication

This is dedicated to my respected mentor, family and friends.

Acknowledgement

To begin with, I would like to thank the Almighty who blessed me with strength, knowledge and good health and has helped me finish the project with effort.

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List of Acronyms

AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
mTOR	Mammalian target of rapamycin
PIN1	Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1
PCNA	Proliferating Cell Nuclear Antigen
MCF7	Michigan Cancer Foundation
ROS	Reactive Oxygen Species
DENA	Diethyl Nitrosamine
HCC	Hepatocellular Carcinoma
RCT	Randomized Controlled Trial
NK	Natural Killer
ECM	Extracellular Matrix
MDSC	Myeloid-Derived Suppressor Cells
ANXA1	Annexin A1
MMP	Matrix Metalloproteinases
JNK	c-Jun N-Terminal Protein Kinase
KSP	Kinesin Spindle Protein
K-RAS	Kirsten Rat Sarcoma Virus
ERK	Extracellular signal-regulated kinase
EZH2	Enhancer of zeste homolog 2
MM	Multiple Myeloma

Chapter 1

Introduction

1.1 Background of cancer and cancer drug development

Cancer has a greater global mortality rate than any other disease, making it one of the deadliest and most stubborn illnesses. The cancer epidemic is a major and growing problem around the world. In 2019, new cases of cancer are anticipated to reach 23.6 million, with an estimated death rate of 10.0 million., according to a recent data analysis. There has been an increase of 26.3% in new cases and a rise of 20.9% in fatalities since 2010 (Kocarnik et al., 2022). The International Agency for Research on Cancer (IARC) forecasts that by 2040 there will be 27.5 million new cases of cancer worldwide. It is assumed that the risk of developing cancer is higher in developing nations than in developed ones because of the lack of resources dedicated to cancer research, treatment, control, and prevention.

Therefore, it is essential to discover new therapeutic approaches that can meet the existing and future difficulties in diagnosing and treating cancer (Kaushik, Ramachandran, Prasad, & Srivastava, 2021).

1.2 Limitations of Conventional Cancer Treatment and Drug Development

In the recent two decades, high-throughput and genomic screening have advanced greatly to detect and recognize novel cancer drugs (Kirtonia et al., 2021). In the conventional approach, the process of discovering and developing cancer drugs typically involves the identification and optimization of lead compounds, which are subsequently subjected to comprehensive pre-

clinical and clinical investigations to evaluate and determine their pharmacological characteristics, antineoplastic activities, and toxicity. This rigorous procedure is both costly and time-consuming. It is estimated that it takes an average of 13 years and an average investment of roughly $1.8 billion USD to move a drug from the laboratory to clinical use. There are currently 10,000 medications that have been submitted for testing in clinical trials. Nevertheless, it is anticipated that a meagre proportion of medications, namely less than 1%, will get to the stage of clinical trials (Kaushik et al., 2021a; Sleire et al., 2017). Only about 5 percent of oncology medications that enter Phase I clinical trials are approved, and only about 1 in every 5,000 to 10,000 potential anticancer treatments receives FDA approval. However, following marketing approval there has been a substantial increase in the pricing of oncology drugs, resulting in a major increase of financial strain on global health economies. According to a study, the increasing expenses and prolonged duration associated with the development of novel drugs provide a significant challenge. Consequently, in cases where drug resistance emerges, individuals suffering from advanced stages of the disease may succumb to their condition before alternative therapeutic options are made accessible. These problems have collectively stimulated the exploration of alternate approaches to enhance success rates, reduce processing time, and decrease costs in the field of cancer medication development (Zhang et al. 2020),

1.3 Drug repurposing as a potential solution

In the given context, the concept of drug repurposing serves as a viable alternative approach to drug development. The strategy of drug repurposing involves the identification of alternative uses for medications that have already been licensed or are currently being investigated. These new uses are typically beyond the intended medical indications for which the treatments were initially developed (Pushpakom et al., 2018). In addition, repurposing pharmaceutical

compounds offers numerous advantages in contrast to the development of entirely novel drugs, with the two most significant benefits being a reduced risk of failure attributed to safety concerns and a shorter duration of the development process. Another advantage is that repurposing the therapeutic indication of an already licensed medicine requires less investment. The repurposing path for medication approval is projected to have an average duration of 3 to 12 years and an associated cost ranging from $40-80 million. Which indicates that this approach is notably more cost-effective when compared to the usual method of drug development. Furthermore, it has been anticipated that the rate of drug approval through the repurposing route is approximately 30%, which is significantly higher compared to the usual approach to drug development, where the approval rate stands at approximately 10%. The fact that the majority of medications being considered for repurposing have undergone thorough extensive safety testing, the repurposing strategy carries a little risk of drug failure, as indicated by the high rate of approval for repurposed drugs. The decreased cost of pharmaceuticals would facilitate the timely and cost-effective delivery of medications to individuals suffering from cancer by pharmaceutical companies. Therefore, it makes sense to look at the possibility of repurposing pharmaceuticals that are already on the market (Kale et al., 2021).

1.4 Aim of the study

The aim of this review is to look deeply into the possible anticancer effects of various non oncology medications and to examine the growing field of pharmacological repurposing for cancer therapy.

1.5 Objectives of the study

This review seeks to accomplish the following goals by conducting a comprehensive analysis of the relevant literature and research studies:

- Introduction to the Field of Drug Repurposing
- Comprehensive reviews of promising cases where repurposed medications have been used successfully for various cancer types in preclinical and clinical settings [***Table 1***]
- Explore synergistic combination
- Summary of challenges and limitations of medication repurposing

SI. No.	Drug name	Class	Type of cancer treat	Mechanism	References
1.	Metformin	Antidiabetic	Breast, Prostate, colorectal and hepatocellular and Pancreatic cancers	↓ IGF-1 signaling pathway, ↓mTOR, activate AMPK.	(Shafiei-Irannejad et al., 2017), (Cejuela, Martin-Castillo, Menendez, & Pernas, 2022)
	DPP4 inhibitor		Breast cancer, colon cancer, prostate cancer	Activate NF-κB, ↓cell cycle regulator pCDC, ↑ glucagon-like peptide-1 (GLP-1)	(Kirtonia et al., 2021).
2.	Statin (Lovastatin, Fluvastatin, Simvastatin)	Cardiovascular drugs	Breast cancer, prostate cancer, Melanoma	↓ CDK2/Cyclin E pathway, ↓ activity of beta-adrenergic receptors and ↓ tumor angiogenesis.	(Sivaprasad, Abbas, & Dutta, 2006), Dale et al., 2006; Weis et al., 2002).

3.	Aspirin	NSAID	Colon cancer	↓COX-1 in platelets, ↓ lipid or protein inflammatory mediator and ↓colorectal tissue COX-2 expression.	(D. Wang & Dubois, 2006).
4.	Mebendazole	Anthelmintic	Ovarian cancer, Pancreatic	↓ microtubule formation, ↓hedgehog signaling pathway.	(Bai et al., 2011; Pinto et al., 2015), (Zhe Zhang et al., 2020).
5.	Levofloxacin	Antibiotics	Multiple myeloma, (N)SCLC, prostate cancer, lymphoma	↓ mTOR signaling pathway, ↓ CDK proteins MMP9 mediated Angiogenesis	(Song et al. 2016).
	Doxycycline		Osteosarcoma, prostate cancer, and mesothelioma cells	↓ Expression of MMP-2 and MMP-9, ↓expression of epithelial-mesenchymal transition (EMT)	(Qin et al., 2015), (Meng et al., 2014), (Sleire et al., 2017).

6.	Chlorpromazine	Antipsychotic	Hepatocellular carcinoma, glioma, leukemia, and melanoma	↑ expression of the cyclin-dependent kinase inhibitor p21, ↑ apoptosis via up-regulation of p53, ↓ of the Akt/mTOR pathway, ↓ mitochondrial ATP production	(Shin et al., 2010, 2013), (Zhelev et al., 2004),
7.	Tricyclic antidepressants	Antidepressant	Small cell lung cancer.	↓ mitochondrial complex III, ↑ apoptosis of glioma, neuroblastoma, and leukemic cells.	(Daley et al., 2005)

Table 1: List of frequently used non oncogenic repurposed drugs and their mechanism of actio

Chapter 2

Methodology

This article presents a comprehensive overview of several licensed medications that exhibit potential for repurposing as anti-cancer agents, encompassing their applications in both cancer prevention and therapy. The data utilized in this study were acquired from peer-reviewed research articles available on credible platforms, as well as from academic papers, publications, and educational websites. A thorough literature search was carried out using various scientific databases such as PubMed, ResearchGate, Springer, Scopus, Elsevier, Nature, ScienceDirect, Google Scholar, Web of Science etc. The search utilized keywords such as "drug repurposing," "drug repositioning," "cancer therapeutics, "pharmacological strategies," and related terms to ensure appropriate finding of relevant articles. The pertinent information was gathered from the chosen article, encompassing the investigated drug candidates, their initial indications, the types of cancer that were looked into, the experimental models employed (*in vitro, in vivo*), and the significant discoveries related to their potential as anticancer agents. Furthermore, the data that was gathered was subjected to analysis and synthesis in order to discover widely repurposed drugs, as well as their mechanisms and prospective efficacy in the treatment of cancer. All the data has been compiled and referenced accurately, which has helped with understanding.

Chapter 3

Potential non-cancer drugs repurposed for cancer treatment and their mechanisms

3.1 Antidiabetic Drugs

The term "diabetes mellitus" is used to refer to a range of metabolic disorders defined by high blood sugar levels that persist over time. The likely contributors to this condition are both decreased insulin secretion and reduced insulin action. It has been found that combining anticancer drugs with antidiabetic drugs of varying types improves cancer treatment outcomes. Several epidemiological studies have found evidence linking diabetes, particularly type 2 diabetes, and cancer (Shafiei-Irannejad et al., 2017).

3.1.1 Metformin

Metformin, additionally known as N′, N′-dimethyl biguanide, is classified as a biguanide oral hypoglycemic agent which is a popular antidiabetic medication (Ben Sahra, Marchand-Brustel, Tanti, & Bost, 2010). Metformin's antidiabetic effects are a result of the drug's ability to inhibit oxidative phosphorylation by inhibiting complex I of the mitochondrial respiratory chain. Consequently, this disruption results in an elevated AMP to ATP ratio. In response to the elevated AMP, enzymes such as 1,6-bisphosphate kinase, fructose, adenylate cyclase, and AMP-activated protein kinase (AMPK) are allosterically activated, decreasing gluconeogenesis, especially in the liver, and enhancing insulin sensitivity (Shafiei-Irannejad et al., 2017). However, metformin is recognized for its extensive anti-cancer capabilities, which are attributed to its ability to modulate mitochondrial bioenergetics and reduce ATP supply. Growing data shows that metformin disrupts number of signaling pathways that involved in the regulation of cancer cell development, proliferation, and death at the molecular level. One

primary method is the activation of AMPK, (Shafiei-Irannejad et al. 2017). Furthermore, the activation of AMP-activated protein kinase (AMPK) not only has metabolic effects but also functions to block the pro-proliferative phosphoinositide 3-kinase (PI3K) pathway, specifically the functional target of rapamycin complex 1 (mTORC1), and activates the pro-apoptotic p53 protein. Also, metformin has been observed to impede survival by many mechanisms, including the prevention of epithelial-to-mesenchymal transition (EMT), enhancement of senescence, and the exertion of anti-survival effects on cancer stem cells (Kale et al., 2021). Therefore, metformin has potential as a cancer treatment. According to a study involving a substantial prospective cohort of 800,000 persons, it was seen that the administration of metformin at a dosage of ≤500 mg/day resulted in a decrease in the occurrence of colorectal and hepatocellular cancers. These findings imply that metformin may have a preventive effect against the development of these specific types of cancer. Based on a comprehensive review of observational studies, persons with diabetes who took metformin as a preventative measure had a reduced chance of developing cancer and a lower risk of dying from cancer. 139 patients with pulmonary adenocarcinoma were enrolled in a recent phase II study because their malignancies carried primary epidermal growth factor receptor (EGFR) mutations (Cejuela, Martin-Castillo, Menendez, & Pernas, 2022). The individuals included in this study was given treatment with tyrosine kinase inhibitors (TKIs), specifically erlotinib hydrochloride, afatinib dimaleate, or Gefitinib, at the normal dosage with or without 500 mg/day of metformin. Overall survival (OS) was approximately doubled by the addition of metformin, and PFS was raised by about a third. Also, women with type 2 diabetes who take metformin regularly for a long time reduce their risk of developing breast cancer (Cejuela, Martin-Castillo, Menendez, & Pernas, 2022). In addition, metformin can block mTOR activity in prostate cancer cells even when AMPK is not involved. Metformin increases p53 activity, which in turn decreases mTOR phosphorylation in this form of cancer. When used with conventional chemotherapeutics,

metformin enhances their efficacy while reducing the hazardous doses required to treat solid tumors (Kale et al., 2021). Thus, the findings from preclinical, clinical and epidemiological studies all point to metformin's efficacy in preventing, treating, and prolonging the lives of people with a wide range of cancers.

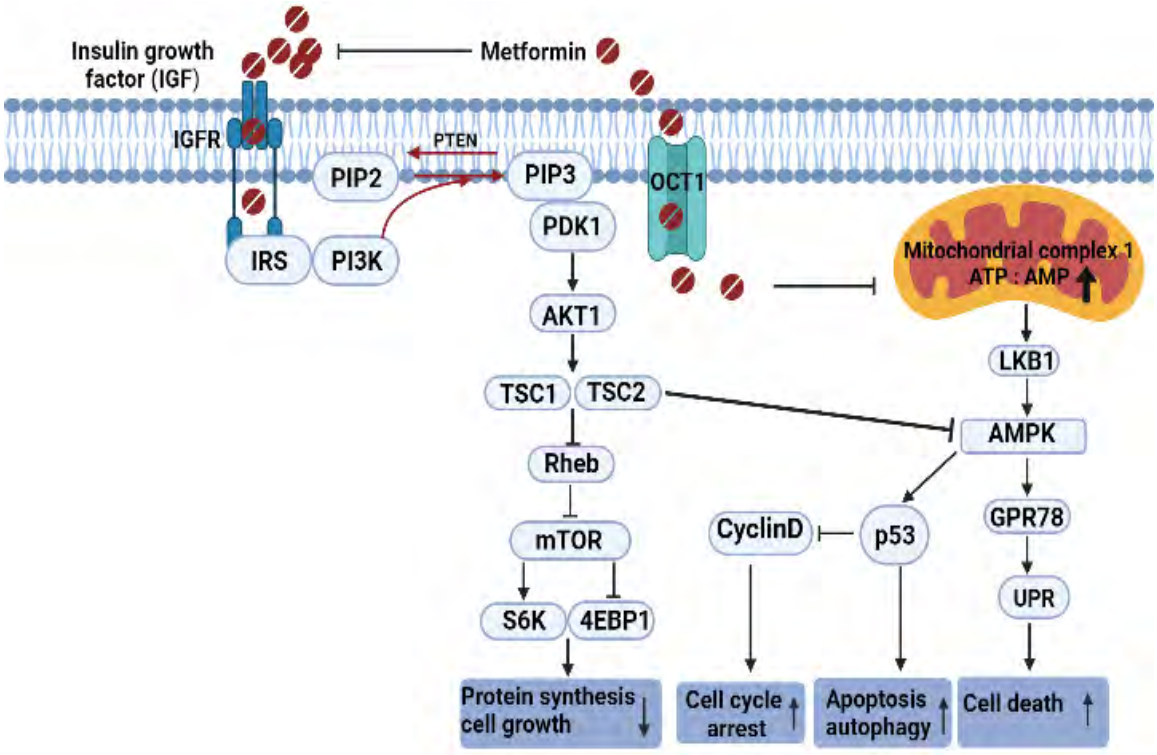

Figure 1: Mechanisms of action of metformin to inhibit human malignancy.

3.1.2 Dipeptidyl peptidase 4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors, including vildagliptin, sitagliptin, and saxagliptin, exhibit the ability to impede the breakdown of glucagon-like peptide-1 (GLP-1), a hormone that plays a crucial role in maintaining glucose homeostasis. Additionally, these drugs have been discovered to possess anticancer properties. The administration of sitagliptin was seen to effectively suppress the activity of DPP4, resulting in the inhibition of EGF-induced

transformation of mammary epithelial cells through the downregulation of PIN1 expression. Additionally, it has the potential to stimulate the production of p21 and p27 while inhibiting the activation of PCNA in MCF7 breast cancer cells. Despite the fact that both sitagliptin and vildagliptin exhibited anticancer activities against malignancies of the colon in vitro, only sitagliptin, when given to rats at doses similar to those used for human treatment, showed a reduction in colon carcinogenesis and blood ROS. The research also showed that reducing inflammation and activating NF-B could have a protective effect against DENA-induced HCC in rats. Patients with type 2 diabetes who take sitagliptin for a year have a lower risk of developing breast cancer, according to a retrospective cohort research (Kirtonia et al., 2021). According to another study, the incidence of prostate cancer in men with type 2 diabetes and oral cancer risk was reduced significantly by sitagliptin, though the effect was found to be dose and duration dependent. The findings of a meta-analysis comprising 72 RCTs suggest that individuals with type 2 diabetes mellitus (T2DM) who get treatment with DPP4 inhibitors exhibit a notably reduced likelihood of cancer development in comparison to patients who are administered a placebo or other chemotherapeutic medicines. Moreover, the growth of lung cancer was effectively suppressed by Vildagliptin through the activation of NK cells mediated by macrophages (Jang et al., 2019). In mice, the administration of vildagliptin demonstrated a notable suppression of autophagy, inhibition of the cell cycle regulator pCDC2, and an increase in apoptosis. Consequently, this resulted in a reduced occurrence and expansion of lung metastases (Jang et al., 2015). Additionally, it inhibited HCC in rats fed a high-fat diet and HCC tumor angiogenesis and growth in mice (Kirtonia et al., 2021).

These studies indicate that DPP-4 inhibitors have potential anticancer effects and they are significant candidates for drug repurposing for cancer.

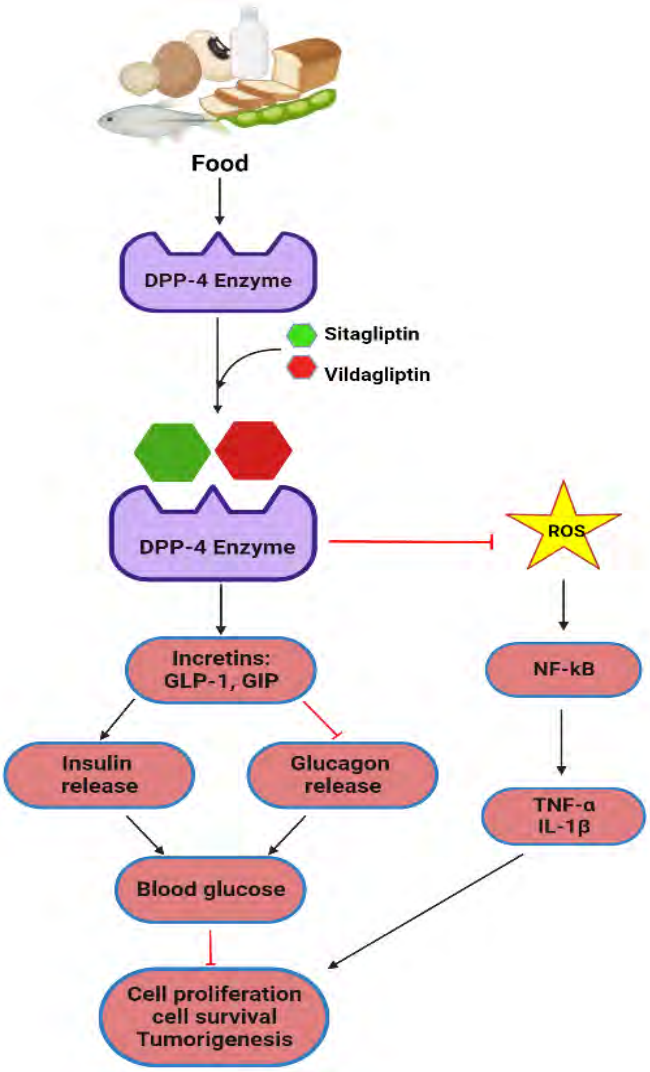

Figure 2: Mechanism of action of DPP-4 inhibitor to inhibit cancer growth.

3.2 Cardiovascular Drug

3.2.1 Statins

Statins are commonly prescribed to patients in order to lower their cholesterol levels due to their ability to act as powerful antagonists of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (HMGCR) (Jiang, Hu, He, Jin, & He, 2021). It lowers blood cholesterol by preventing the production of geranylgeranyl pyrophosphate, isoprenyl and farnesyl

pyrophosphate groups via suppression of the mevalonate pathway's HMG-CoA reductase. Which indicates that the administration of statins leads to alterations in the signaling G proteins that are linked to cell proliferation, migration, and survival signaling pathways. Consequently, these modifications have an effect on the anticancer properties of statins (Dale, Coleman, Henyan, Kluger, & White, 2006; Weis et al., 2002). However, statins have been observed to exhibit a slowing effect on the proliferation of cancer cell lines in experimental studies. For instance, the compounds lovastatin, Fluvastatin, and simvastatin have demonstrated the ability to inhibit the G1/S transition in prostate cancer by blocking the CDK2-CyclinE pathway (Sivaprasad, Abbas, & Dutta, 2006). Also, high doses of statins were proven to reduce tumor vascularization in mice with cancer as the adhesiveness of malignant cells to ECM proteins is impeded through the inhibition of integrin's binding capability. In addition, *in vivo* orthotopic solid tumor xenograft models, including colon cancer, revealed the effectiveness and anticancer actions of statins (Cho et al., 2008). Furthermore, statins, especially simvastatin, have shown promise in the treatment of solid tumors in clinical trials The results of a controlled trial suggest that the consumption of simvastatin at a dose of 40 mg/day or higher for a period of 2 to 5 years led to a notable decrease in the incidence of colorectal cancer. Another study found that individuals diagnosed with stage IV non-small cell lung cancer (NSCLC) who adhered to a consistent regimen of statin medication exhibited a notably elevated rate of survival Research like this suggests that statins could be used to help reduce the risk of cancer in people who are more likely to get the disease (Kale et al., 2021).

3.3 NSAIDS

The Food and Drug Administration (FDA) initially approved aspirin (acetylsalicylic acid) to treat pain and fever, and then expanded its use to include the prevention of stroke and cardiovascular disease (Gaziano et al., 2018). The primary function of nonsteroidal anti-

inflammatory medicines (NSAIDs) is pain relief and inflammation prevention through the inhibition of cyclooxygenase-2 (COX-2). Several NSAIDs, when taken in higher doses, have been shown to inhibit the development of tumor cells and promote programmed cell death; this suggests that they may be useful as an anticancer therapy. According to a meta-analysis NSAIDs inhibit tumor growth and slow the spread of metastases (Zhao, Xu, & Li, n.d.).

3.3.1 Aspirin

Since 1968, researchers have looked into the possible anticancer effects of aspirin, a drug frequently employed to treat pain (Zhao et al., n.d.). A wide range of studies have been undertaken to determine the anti-carcinogenic capabilities of aspirin across diverse cancer kinds. These investigations have identified various molecular mechanisms underlying its effectiveness. For instance, in colorectal and esophageal cancers, aspirin has been found to exert its anticancer effect by inhibiting the activity of cyclooxygenase (COX). In osteosarcoma, it blocks NF-κB transcriptional activity by targeting COX-2 gene transcription. Moreover, in prostate cancer, aspirin suppresses IκB kinase-β, thereby modulating the signaling of the mTOR. Additionally, in colorectal cancer, it activates AMPK, which contributes to its anticancer properties (Din et al., 2012). Aspirin blocks the enzymes cyclooxygenase (COX) 2 and cyclooxygenase-2 (COX-2), which play a key role in cancer-related inflammation by producing prostaglandins including prostaglandin E2 (PGE2) (D. Wang & Dubois, 2006). Cyclooxygenases (COXs) contribute to the production of prostaglandin E2 (PGE2), which facilitates the proliferation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). These immune cell populations play a role in suppressing the immune response to cancer within the tumor microenvironment. Therefore, the inhibition of cyclooxygenases (COXs) has the potential to hinder the proliferation of MDSCs. Studies also revealed that aspirin suppresses not only COX-1/2, but also other inflammatory cytokines including NF-kB,

and also interferes with pro-survival ERK signaling in cancer cells. Overexpression of NF-kB and ERK signaling is common in MM cells (Kale et al., 2021). Furthermore, it has been demonstrated through study that certain medications containing aspirin exhibit anticancer properties in the cancerous cells of the colon and pancreas. This effect is achieved by activating ANXA1, a protein that potentially impedes the binding of NF-kB to DNA. Consequently, this mechanism promotes enhanced apoptosis and reduced proliferation. (Zhang et al. n.d.). The "Health Professional Follow-up Study" (1986-2008) and the "Nurses' Health Study" (1976-2008) are two large prospective studies that support the hypothesis that continuing to take aspirin following a diagnosis of MM decreases the risk of death overall and death from MM specifically. These studies also claim that taking 325 mg of aspirin five or more times per week reduces the incidence of MM by 40%. However, the risks associated with long-term aspirin use must be considered. These include an increased risk of stomach ulcers, heartburn, and bleeding (Kale et al., 2021).

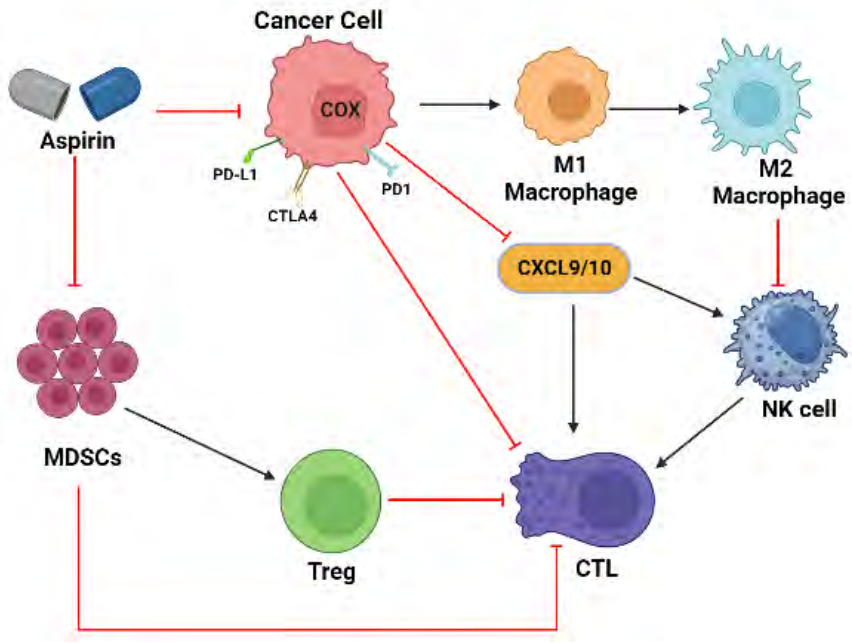

Figure 3: Mechanism of action Aspirin to inhibit cancer cell proliferation.

3.4 Anthelmintic

3.4.1 Mebendazole

Mebendazole (MBZ) is a drug that has been approved by the FDA for use in anthelmintic therapy. This medication has an outstanding safety record when it comes to its use in humans. Mebendazole is effective against intestinal helminthiasis because it inhibits tubulin polymerization (Bai et al., 2011). Mebendazole has been shown to be effective against multiple forms of human cancer in both *in vitro* and *in vivo* trials (Nygren et al., 2013). During the early 2000s, there were reports indicating that mebendazole inhibited the growth of non-small cell lung cancer by causing cell cycle arrest in response to tubulin depolymerization. Following this, the primary mechanism of action of mebendazole against glioblastoma and stomach cancer was suggested to be tubulin depolymerization (Bai et al., 2011; Pinto et al., 2015). Significantly, it was demonstrated that the administration of mebendazole resulted in increased sensitivity of cancer cells to radiotherapy through the regulation of DNA damage response proteins. Researchers found that mebendazole enhanced the effectiveness of radiotherapy by blocking the nuclear import of the DNA-damage repair proteins Chk2 and Nbs1. In addition to its chemo preventive effects, mebendazole has also been shown to have radio-sensitizing activity in breast cancer. Additionally, it has been observed to decrease the proportion of stem-like cells through modulation of the hedgehog pathway, potentially by regulating glioma associated oncogene homolog 1 (GLI1), a downstream mediator of the hedgehog pathway, in response to DNA damage (Zhe Zhang et al., 2020). While MBZ inhibits tubulin polymerization in lung cancer, it promotes apoptosis in melanoma cells by phosphorylating BCL-2 and so inactivating BCL-2. Combination therapy with mebendazole and a gemcitabine derivative was cytotoxic to chemo resistant SKBr-3 Cells from breast adenocarcinoma (Coyne, Jones, & Bear, n.d.). In addition to acting as a Hedgehog inhibitor in medulloblastoma, MBZ was shown to have high binding affinities and hence possibly be an inhibitor of numerous kinases and

oncogenes such as ABL and BRAF in colon cancer cell lines (Nygren et al., 2013b). Malignant gliomas are typically treated with temozolomide, which can be coupled with mebendazole. This combination therapy was more effective than temozolomide alone in suppressing tumor growth in both a xenograft and a syngeneic model of glioblastoma (Bai et al., 2011). Two published case reports have documented the use of mebendazole as a treatment for adrenocortical carcinoma and colon cancer (Nygren & Larsson, 2014; Zhe Zhang et al., 2020). These results demonstrated a significant reduction in cancer metastasis after treatment with mebendazole, with no apparent side effects. Mebendazole's low cost, minimal toxicity, and proven anti-cancer impact all point to its potential as an adjuvant therapy in a variety of malignancies.

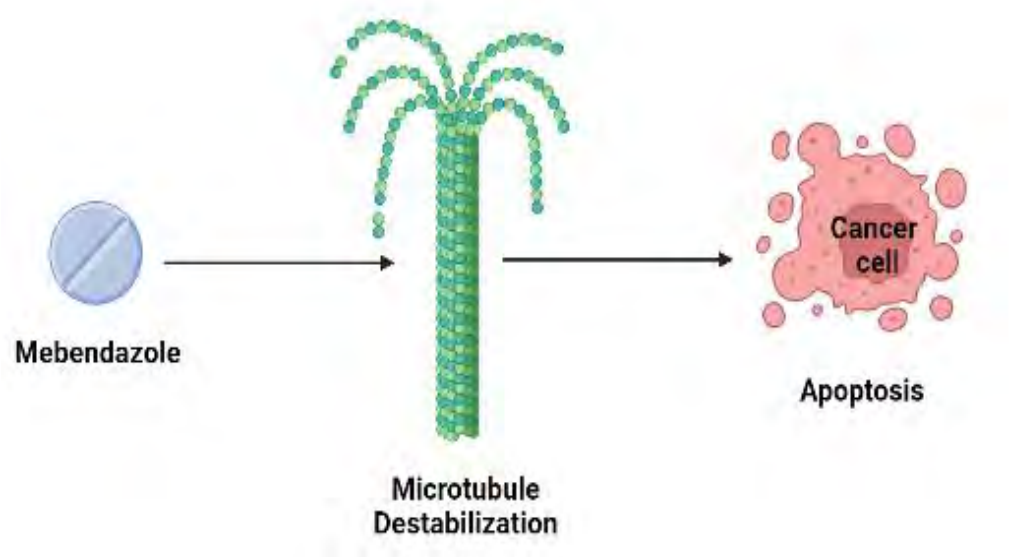

Figure 4: Mechanism of Mebendazole to induce cancer cell apoptosis.

3.5 Antibiotics

3.5.1 Levofloxacin

In 1996, the FDA approved levofloxacin, an antibiotic derived from Lupinus luteus and marketed under the brand name LEVAQUIN. Levofloxacin, an antibacterial medication of the third generation of the fluoroquinolone class, works by inhibiting DNA replication in bacteria. Its clinical application is widespread for treating mild to severe infections caused by susceptible bacteria. Levofloxacin, a repurposed antibiotic, appears promising as a potential cancer treatment, although further research is needed (Wang et al. 2021). According to a study, it was found that Levofloxacin demonstrates antiproliferative and apoptotic properties in breast cancer cells by inhibiting mitochondrial biogenesis. This inhibition is accompanied by the deactivation of two signaling pathways, namely PI3K/PKB/mTOR and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (Song et al. 2016). Additionally, it was discovered that the administration of levofloxacin successfully blocked the development of lung cancer cells and triggered the process of apoptosis. Levofloxacin was found to exert its inhibitory effects on the mitochondrial electron transport chain complex, resulting in the subsequent blockade of mitochondrial respiration. This inhibition led to a reduction in adenosine triphosphate (ATP) generation and an elevation in the levels of reactive oxygen species (ROS), including mitochondrial superoxide and hydrogen peroxide (M. Song et al., 2016). In 2014, a patent application titled "Uses of antibiotic in preparing pharmaceutical composition for treatment of cancer" was submitted for Levofloxacin. Nevertheless, clinical trials were conducted to investigate the inhibitory effect of minimal-risk neutropenic fever and bacteremia in human malignancies, rather than focusing on the direct anticancer effect (Jung et al. 2021).

3.5.2 Doxycycline

Doxycycline is a tetracycline-class antibiotic that exhibits efficacy against a diverse spectrum of infectious illnesses. In the early 1990s, certain tetracyclines were demonstrated to effectively inhibit angiogenesis (Tamargo et al., 1991). It was later revealed that doxycycline could slow the expansion of cancer cells, including those of the prostate, osteosarcoma and mesothelioma varieties. In addition, previous studies have reported the presence of pro-apoptotic properties of doxycycline in both pancreatic cells and leukemic cells (SON et al., 2009; H. Song et al. 2014). The administration of doxycycline has been observed to result in the down-regulation of MMP-2 and MMP-9 expression in leukemic and colorectal cancer cells, subsequently leading to the suppression of cellular invasion. In a preclinical investigation examining bone metastases originating from breast cancer, the administration of doxycycline was observed to elicit a reduction in tumor size inside both the osseous structures and the adjacent soft tissue. Also, the inhibition of MMP-2/9 has been observed to result in a reduction in metastasis in animal models of prostate cancer and oral squamous cell carcinoma (Sleire et al., 2017). In addition, the administration of doxycycline has been shown to reduce the expression of epithelial-mesenchymal transition (EMT) markers in cells of lung cancer and hepatocellular carcinoma. This reduction leads to a reversal of a phenotype that promotes metastasis (Qin et al., 2015). According to a subsequent study, it was determined that doxycycline had efficacy in specifically targeting glioblastoma by generating dysfunctions in the mitochondria and oxidative stress (Tan et al., 2017).

3.6 Antipsychotics

Antipsychotic medications are commonly administered to address many psychotic disorders, including but not limited to Tourette's syndrome, acute mania, schizophrenia, bipolar disorder, chronic psychosis with hallucinations, delusions, and paranoia, and tics. The antipsychotic

effects of typical antipsychotic medications, including chlorpromazine (CPZ), haloperidol, trifluoperazine, fluphenazine, thioridazine, and perphenazine, are achieved through the inhibition of dopamine D2 receptor activity. Epidemiological investigations conducted on a substantial cohort of individuals diagnosed with schizophrenia have revealed a decreased occurrence of cancer among patients receiving treatment for psychosis. A comprehensive study conducted across several regions including the United States, Israel, Europe, Asia, and Africa revealed a notable decrease in standardized incidence ratios of cancer among individuals with schizophrenia who received treatment for psychosis, in comparison to cancer patients without schizophrenia (Cohen et al., n.d.;). These initial investigations brought attention to the antineoplastic characteristics of neuroleptic medications.

3.6.1 Chlorpromazine (CPZ)

Chlorpromazine is a medicine used for the treatment of psychiatric diseases that has been around for sixty years. This chemical inhibits the stimulating effects of dopamine at the post-synaptic level by blocking the D2 dopamine receptor (DRD2) in the brain. DRD2 is overexpressed in glioblastoma multiforme (GBM), particularly in glioma-initiating cells, where it controls homeostasis by boosting cellular plasticity and tolerance to hypoxia. In addition, CPZ's ability to block cancer cell development via multiple mechanisms has been shown in multiple studies. According to research conducted in the early 1990s, chlorpromazine may reduce the incidence of prostate cancer in males with schizophrenia (Sleire et al., 2017). Hepatocellular carcinoma, glioma, leukemia and melanoma are only some of the cancers in which chlorpromazine and other phenothiazines have been shown to limit tumor growth (Shin et al., 2010, 2013; Zhelev et al., 2004). Interference with mitochondrial activities and changes in the expression of many proteins involved in the cell cycle have been implicated as primary

mechanisms driving these effects. CPZ induces G2 or M-phase arrest in glioma cells through elevated production of the cyclin-dependent kinase inhibitor p21 (Shin et al., 2010). Moreover, chlorpromazine causes apoptosis in colorectal cancer cells by increasing p53 expression (Sleire et al., 2017). The mitogen-activated protein kinase (MAPK) family member JNK is essential for p53 activation. Chlorpromazine also inhibits normal lymphocyte viability at amounts that cause death in leukemic cells via decreasing mitochondrial ATP generation and DNA polymerase activity (Zhelev et al., 2004). Furthermore, when CPZ was tested in glioma cells, it was reported to promote autophagy via blocking the Akt/mTOR pathway (Shin et al., 2013). Ineffective centrosome separation and subsequent mitotic arrest are the results of CPZ's inhibition of the mitotic kinesin KSP/Eg-5. Also, CPZ causes K-Ras to become more active by decreasing its interaction with the plasma membrane. In addition, CPZ inhibits K-Ras's ability to associate with the plasma membrane, which results in elevated K-Ras in the cytoplasm and internal membranes and, ultimately, growth arrest and death. Notably, at dosages that do not influence the viability of normal lymphocytes (Zhelev et al., 2004), chlorpromazine lowers mitochondrial ATP synthesis and DNA polymerase activity in leukemic cells, leading to death. CPZ is also found to boost autophagy by blocking the Akt/mTOR pathway in glioma cells (Shin et al., 2013).(Sleire et al., 2017)

These results suggest that CPZ may have anti-tumor properties. The growth of tumors in numerous types of cancer, including hepatocellular carcinoma, glioma, melanoma, and leukemia, was found to be suppressed by additional antipsychotic medications of the same class (Kaushik et al., 2021). Therefore, similar and dissimilar neuroleptic medications were tested for their possible anti-cancer effects

3.7 Antidepressant

The prevalence of depression among the global population is estimated to be 20%, leading to significant research and development efforts focused on the development of antidepressant medications. Antidepressants, originally developed to treat the symptoms of depression and other mood disorders, have shown surprising qualities outside of their original use. Scientists are conducting research into the potential of these medications to precisely affect different cellular pathways and mechanisms associated in the growth and viability of cancer. According to studies, preclinical investigations have revealed that certain antidepressant medications possess the ability to inhibit cancer growth through many pharmacological processes. These mechanisms encompass the regulation of cell proliferation, metastasis, cell cycle progression, programmed cell death (apoptosis), cellular self-degradation (autophagy), tumor immune response, and oxidative stress (’Song, 2021).

3.7.1 Tricyclic Antidepressant

TCAs, or tricyclic antidepressants, are a class of drugs distinguished by their molecular structure, which consists of three fused rings. These medications are commonly employed in the treatment of clinical depression and various mood disorders. While the precise process remains incompletely understood, the impacts of these substances are partially facilitated by their ability to hinder the absorption of amine neurotransmitters, including serotonin and norepinephrine transporters. Additionally, there have been suggestions that these pharmaceutical substances alter the plasticity of neurons in response to the observed atrophy and cellular death associated with depression. It is important to highlight that other investigations have revealed the antineoplastic effects of antidepressants. The mechanism of action of tricyclic drugs, such as clomipramine, in exerting their antineoplastic effect has been demonstrated to involve the inhibition of mitochondrial complex III. This inhibition leads to a

reduction in oxygen consumption, ultimately resulting in the induction of apoptosis through the activation of caspases (Daley et al., 2005). The induction of apoptosis in glioma and neuroblastoma cells is suggested to entail not only caspase activation, but also signaling through c-junction and the release of cytochrome c from mitochondria. Previous studies have also documented comparable results in the context of leukemic cells. Research findings indicate that tricyclic antidepressants (TCAs) may have the potential to serve as a secondary treatment option for individuals with small cell lung cancer (SCLC) who develop resistance to cisplatin/etoposide chemotherapy. Moreover, Amitriptyline, a tricyclic medication, is proposed as a therapeutic agent for oxidation, wherein it has the dual capability of enhancing reactive oxygen species levels while reducing antioxidant levels (Sleire et al., 2017).

Chapter 4

Repurposed drugs in combination with various agents/drugs

In addition to these pharmaceutical agents, certain non-oncological medications have been investigated for their potential application in combination therapy for cancer. In addition to those already mentioned, researchers might not consider additional medications for drug repurposing screening due to their inadequate anticancer activity at known acceptable plasma drug concentrations documented in earlier indications. Luckily, there remains a possibility for the discovery of those medications that exhibit potential efficacy at elevated dosages. Drug combination therapy has the potential to take advantage of such effects and repurpose these medications, creating a synergistic impact by targeting alternate signaling pathways linked with particular disease hallmarks, rendering cancer cells more vulnerable to other cytotoxic agents. Another potential benefit of medication combination therapy is lower overall drug dosages. Additionally, multifactor and polygenic diseases have been linked to Neoplastic illness, highlighting the need for pharmacological combination therapy to target cancer-related signaling networks (Kirtonia et al., 2021). Combining medications with complementary modes of action is standard practice in clinical practice today. Here are some examples of repurposed drug in combination therapy for cancer is shown in

Table 2: List of repurposed drugs that used in combination with others agents

Combination of repositioned drugs	Combined drug classes	The synergistic impact of drugs on various forms of human malignancies	References
Thalidomide and Dexamethasone	Immunomodulatory and Corticosteroid	Inhibit angiogenesis, reduce the production and activity of abnormal plasma cells in multiple myeloma.	(Zhang et al., 2020)
Ribavirin and Interferon-α	Antiviral and Immunomodulators	Modify ERK, MNK1, and EZH2 in neoplasia.	(Gonzalez-Fierro & Dueñas-González, 2021)
Doxycycline and Vitamin C	Antibiotic and vitamin	Increase the production of hydrogen peroxide and promote cancer cell death in Breast Carcinoma	(Garg et al., 2017)
Digoxin and Trametinib	Cardiac glycosides. and kinase inhibitors.	Inhibit H1F- α, inhibit MEK. Wild metastatic melanoma	(Kirtonia et al., 2021)
Metformin and Atorvastatin	Antidiabetic and Statin	Synergistic in prostate carcinoma	(Wang et al., 1247)

Clotrimazole and Imatinib	Antifungal and Kinase inhibitor	Synergistic in thyroid carcinoma	(Kirtonia et al., 2021)
Aspirin and anti-PD-L1 antibody	NSAID and Immune Checkpoint inhibitor	Synergistic in colorectal cancer	(Hamada et al., 2017)
Disulfiram and Copper	Antabuse and Trace element.	Synergistic in glioblastoma	(Kirtonia et al., 2021)

Table 2: List of repurposed drugs that used in combination with others agents

Chapter 5

Challenges and limitations of drug repurposing for cancer treatment

In cancer treatment, drug repurposing is already widely used with the goal of redeploying existing molecules for new applications. Drug repurposing has had some early achievements, as discussed in this review. However, not all drug candidates can be repurposed successfully; examples include Latrepirdine, Ceftriaxone, and Topiramate, most of which failed in late-stage, phase III trials. As with the development of entirely new medications, it is inevitable that some late-stage candidates will fail. However, the toxicity that might otherwise have caused these failures has been mitigated by the thorough evaluation of the candidates' safety profiles (Pushpakom et al., 2018; Zhang et al., 2020)

Additional factors contributing to failures within the context of drug repurposing are associated with specific barriers unique to this field. These barriers encompass concerns surrounding patents, inadequate funding for clinical trials, absence of targeted therapeutic approaches, unfair prescription practices as well as unavailability of data (Zhang et al., 2020).

5.1 Difficulty in obtaining legal and intellectual property right

Drug repurposing is hindered by many legal and intellectual property issues. The challenges related to the process of obtaining a patent for a novel repurposed indication, as well as the subsequent enforcement of patent rights, constitute significant barriers in promoting drug repurposing. These challenges exert a substantial influence on the expected financial profits derived from the repurposed product (Pushpakom et al., 2018).

The protection of a novel repurposed medical use of an approved medicinal molecule can be accomplished in the majority of prominent pharmaceutical markets, granted that the new medical application demonstrates novelty and innovation. Nevertheless, some potential uses for repurposing that have previously been documented in the professional literature are now being utilized in clinics as off-label, unregistered usage. Despite the lack of validation from controlled clinical trials, the dissemination of such information to the public domain has implications for novelty and, subsequently, the potential for patentability. To secure a granted patent for a novel repurposed medical use, the patent holder must additionally furnish data within the patent application that supports the drug's efficacy as a viable treatment for the specific new indication in question (Pushpakom et al., 2018).

While it is possible to get a patent for a new indication for an off-patent drug, implementation may be an issue if the new indication makes use of strengths and dosage forms that are already on the market. This phenomenon occurs due to the widespread availability of generic drugs from various manufacturers, which allows doctors to prescribe them for non-patented reasons. However, off-label use may be constrained if the repurposed indication calls for a novel formulation and/or dosing regimen that is not readily achievable with the already available generic forms of the medicine. In light of the mentioned challenges, it is crucial to deliberate on the methods and degree to which intellectual property can be safeguarded for a reused output during the initial stages of the project. (Breckenridge & Jacob, 2018; Pushpakom et al., 2018).

5.2 Inadequate funding for clinical trials

Repurposing cancer medications for wider usage, commercialization, and approval is a challenging task. The primary barrier to the clinical development and approval of repurposed pharmaceuticals is the economic aspect. Due to concerns regarding intellectual property rights, the business community exhibits less enthusiasm in pursuing the development of this particular

pharmaceutical, as their primary objective is to secure substantial profits on their investments. It can be stated that among the 190 registered clinical trials examining the 72 drugs listed in the Redo project, the majority (67%) are sponsored by University or Hospital entities. Additionally, 28% of these trials are sponsored by research Institutes or non-profit organizations. A smaller percentage of trials (3%) receive sponsorship from small or medium-sized pharmaceutical companies, while 2% are sponsored by government entities. Notably, only 1% of the trials receive sponsorship from large pharmaceutical companies. The failure to successfully commercialize the resulting product might be caused by challenges in identifying suitable commercial partners, as well as an abundance of financial and resource allocation(Gonzalez-Fierro & Dueñas-González, 2021; Pantziarka et al., 2018).

5.3 Unavailability of data and compound

While the utilization of the open-source paradigm is increasingly becoming prevalent in the drug discovery community, there remains a restricted availability of some types of valuable data, such as clinical trials, to the public. Despite the absence of accessibility concerns, certain forms of data, such as imaging data, provide challenges in terms of data mining, integration, and manipulation or may be provided in a non-standardized format (Pushpakom et al., 2018). The computational demands of integrating various forms of data have been demonstrated, as it enhances the analytical capabilities (Novac, 2013).

The process of drug repurposing entails the systematic examination and potential reevaluation of drugs that have already been approved for marketing or have been previously considered for clinical research but were ultimately abandoned. The acquisition of pharmacodynamic, pharmacokinetic, toxicity, and safety data, along with any additional pertinent data related to the drug or drug candidate, is crucial. At present, a number of drug repositories are available, but no such resources exist for drug candidates. The possible repurposing of a medicine may

face significant challenges if the intended new use of the drug is not aligned with the organization's primary focus on a specific disease area. Moreover, there could be problems with compound availability when using generic active pharmaceutical ingredients, especially if the component has been removed from international markets. It may be difficult to find a trustworthy vendor under these conditions (Novac, 2013)

5.4 Unfair prescription practices

In general, doctors should base their prescription recommendations on data from controlled clinical trials, and they should use generic or repurposed pharmaceuticals whenever it is suitable. Despite this, the pharmaceutical industry possesses the capacity to exert influence through substantial financial investments in medication promotion, targeted marketing efforts towards physicians, and advertising campaigns aimed at consumers. Thalidomide serves as an appealing example of the potential issues that can arise (Zhang et al., 2020). Initially, this substance was administered for its sedative and antiemetic effects, due to its low cost and safety profile. However, it has more recently been repurposed for the treatment of multiple myeloma. Two randomized clinical studies were conducted to evaluate the therapeutic regimen of melphalan–prednisone–lenalidomide with that of melphalan–prednisone–thalidomide. The results of these trials indicated that there was no observed survival advantage associated with the melphalan–prednisone–lenalidomide regimen ((Stewart et al., 2015). Nevertheless, lenalidomide, as opposed to thalidomide, has been authorized as the established treatment, despite its significantly higher cost, which is approximately 43 times greater than that of thalidomide. Undoubtedly, the implementation of cost-effective pharmaceutical interventions includes the prescription of more affordable medications that possess comparable therapeutic efficacy(Zhang et al., 2020)

5.5 Lack of targeted therapy

Despite the several benefits linked to drug repurposing, the repositioning of current drugs presents specific barriers that must be resolved prior to their effective utilization in clinical settings. As a result of the prevailing focus on targeted therapy, the number of repurposed medications that have been discovered to specifically target cancer cells remains limited. In contrast, it is notable that a significant proportion of prospective anti-cancer medications with repurposing potential are specifically designed to address the complex nature of the tumor microenvironment. Drugs that have been repurposed may also have immunomodulatory and other off-target effects, which is another potential drawback. Due to the broad spectrum of the targets of these drugs, it is uncertain that they may be employed as monotherapy in the field of cancer treatment (Chartier et al., 2017; Kaushik et al., 2021).

Chapter 6

Conclusion and future perspective

Human cancers exhibit substantial variation and hence necessitate the implementation of various therapeutic approaches. Over the past two decades, advanced cancer treatments have been discovered. Despite that, many cancer patients are untreatable due to their resistance to current treatment, which is a big challenge for researchers and doctors. Moreover, due to a lack of funds, many countries cannot afford chemotherapy drugs. Thus, drug repositioning is a very promising strategy for accelerating and cost-effectively developing innovative anticancer drugs. As discussed in above several classes of drugs have been investigated for their potential to increase cancer cell or cancer stem cell (CSC) sensitivity; these drugs have been shown to inhibit cell proliferation, dissemination, invasion, and trigger apoptosis and cell cycle arrest by targeting well-studied carcinogenesis-related pathways. However, FDA has authorized the use of some drugs to treat cancer in humans such as thalidomide and Raloxifene. Also, a significant inverse link between some drugs and cancer risk was found in different studies as mentioned above that included metformin, statins, NSAIDs and aspirin. The results point towards the potential for these drugs to be approved for use in the treatment of cancer in the future.

The use of non-cancer drugs to treat cancer has attracted scientific attention due to its proven effectiveness and this strategy may speed up and reduce the cost and time needed to identify novel cancer therapies. Though numerous medicines have demonstrated anticancer activity, only a few selected drugs have been successfully implemented into clinical practice. Others are facing challenges in their trials or are unable to acquire marketing authorization due to regulatory hurdles. Hence, it is essential to implement necessary actions with proper guidelines

and strategy in order to unlock the latent potential of drug repurposing and enhance the possibilities of more effective cancer treatment.

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