Repurposing Drugs for Overcoming Therapy Resistance in Colon Cancer – A Review

Mahdi Darvishi [1], Amir Mohammad Chekeni [2], Mohammad Fazelhosseini [1], Zeenat Iqbal [3*], Mohd Aamir Mirza [3*], Mohammed Aslam [4], Esra Tariq Anwer Bayrakdar [4]

Abstract

Colorectal cancer is a common type of cancer worldwide. Colorectal cancer is a prevalent form of cancer that is observed globally. The survival prospects for individuals with advanced stages of this disease are notably diminished. The chance of getting colorectal cancer is 4% to 5%. Getting older, having chronic illnesses, and certain lifestyle choices raise the risk of getting colorectal cancer. Surgery, as well as neoadjuvant radiation treatment (for those affected by rectal cancer) and adjunctive chemotherapy (for stage III/IV colon cancer patients and high-risk stage II colon cancer patients), stand as the most employed therapeutic interventions. Treating CRC has improved, but the medicines are expensive and have side effects. Therefore, alternative methods that are more affordable and still effective need to be explored. The use of existing drugs to treat diseases is becoming more popular due to high attrition rates, economic burden, slow drug discovery, and development. Many methods have been proposed to find repurposed therapeutic candidates, which can save time and money. Repurposing drugs is more successful and efficient than creating new drugs for rare diseases. Using existing drugs for cancer treatment is a major priority. Non-cancer drugs should not be overlooked since they have the potential to address both identified and unidentified weaknesses in cancer. Unlike targeted therapy, old generic drugs used in multiple ways can benefit patients. This review delves into the present body of evidence regarding the utilization of established medications as a plausible therapeutic avenue for patients suffering from CRC. The focus is to illustrate the possible competitors and their complex ways of functioning, including medications that have the ability to combat malaria, parasitic infections, inflammation, high blood pressure, high cholesterol levels, and diabetes.

Keywords: Colon Cancer, Colorectal cancer (CRC), Drug Repurposing, Therapy Resistance, Anti-Helminthic Drugs, Nonsteroidal Anti-Inflammatory Drugs, Anti-Hypertensives, Antiarrhythmic Drugs,

Significance | Oncology research seeks new therapies for aggressive CRC, utilizing repurposed drugs for accelerated and safer treatment approaches.

*Correspondence. Mohd Aamir Mirza and Zeenat Iqbal at Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi 110062, India
E-mail: aamir_pharma@yahoo.com; zeenatiqbal@jamiahamdard.ac.in

Editor Md Shamsuddin Sultan Khan And accepted by the Editorial Board Feb 8, 2024 (received for review Nov 20, 2023)

Introduction

Colorectal cancer was infrequently identified decades ago (Dekker, *et al.* 2019). Among people of all ages and genders worldwide, colorectal cancer (CRC) is considered the third most common form of cancer, and it has become a leading cause of cancer-related deaths, coming in second place (Sung, *et al.* 2021). It is responsible for 9.4% of all deaths. Every year, more than 1.1 million people are diagnosed with CRC, and more than 600,000 people die as a result of the disease (Siegel, *et al.* 2021). In the United States, there were

Author Affiliation.
[1] School of pharmaceutical education and research, Jamia Hamdard, New Delhi-110062.
[2] Bachelor of Nursing, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi 110062, India
[4] Pharmacy Department, Tishk International University, Erbil, Kurdistan region, Iraq.

Please cite this article.
Mahdi Darvishi, Amir Mohammad Chekeni, Mohammad Fazelhosseini et al., (2024). Repurposing Drugs for Overcoming Therapy Resistance in Colon Cancer – A Review, Journal of Angiotherapy, 8(2), 1-23, 9423

approximately 100,000 new cases and 50,000 fatalities in 2021. It is anticipated that by 2035, there would be 2.5 million instances globally (Dekker, *et al.* 2019) . The frequency of this phenomenon exhibits significant variations worldwide and is intricately linked to the attributes of what is commonly referred to as the Western way of life. In contrast to women, men are disproportionately susceptible, and the prevalence notably surges with advancing age(Brenner, *et al.* 2014). Inclination towards colorectal cancer (CRC) appears to be more prevalent among the younger generation, possibly attributed to an increased occurrence of certain risk factors including inadequate dietary habits, reduced physical activity, and an uptick in obesity rates (Wild, *et al.* 2020). The majority of cancers start with polyps. Over the course of 10-15 years, this process begins with aberrant crypts, proceeds to preneoplastic lesions (polyps), and eventually to colorectal cancer. Colorectal cancer is diagnosed by assessment or screening of symptomatic people. Though many cases of colon cancer arise gradually over time as a result of histological, morphological, and genetic changes. This has made it possible to detect and screen for precancerous polyps in individuals with average risk of developing colorectal cancer (CRC), which has the potential to drastically lower the incidence of CRC(Hijazi, *et al.* 2023). Clinical research have shown a median overall survival of 30 months in individuals with metastatic disease during the past 20 years, a significant improvement in survival. Surgery is used to remove the tumor and local lymph nodes in stage I CRC. Over the past two decades, there has been a notable advancement in medical studies which has resulted in a substantial increase in the average life expectancy of individuals suffering from a spreading sickness, with a median survival rate of 30 months. Stage II CRC is not frequently treated with adjuvant chemotherapy. Treatment options for stage IV colon cancer include radiofrequency ablation, palliative surgery, immunotherapy/checkpoint inhibitor treatment, chemotherapy, targeted therapy, and targeted therapy. The list of treatments for different stages of CRC according to stages along with the 5-year survival rate in each stage is outlined in **Table 1.**

Drug resistance is presently a significant obstacle in the field of cancer therapy. Despite the potency of commonly used medications, they often fail to produce a comprehensive and long-lasting tumor response, consequently resulting in treatment resistance and the reoccurrence of tumors (Chatterjee and Bivona 2019). Long-term patient survival is hampered by drug resistance (Nikolaou, *et al.* 2018, Hassan et al. 2018). Unfortunately, medication resistance is still one of the reasons for CRC patients' dismal survival rates. A deeper knowledge of inherent and acquired resistance to treatment is extremely beneficial to medication development (Van der Jeught, *et al.* 2018). The most recent achievements in drug repurposing for the treatment of colon cancer have been examined in this study.

Repurposing approved drugs in colon cancer:

The practice of drug repositioning, which involves using a medication for purposes different from its original intended use, is gaining momentum(Ali, *et al.* 2011)((Ahmad, *et al.* 2021) . Repurposing "old" medications to treat both common and unusual ailments is more prevalent because to high attrition rates, expensive prices, and the slow research and production of new treatments((Ahmad, *et al.* 2023). "The use of risk-free compounds has the potential to minimize total development costs and shorten development time, which makes the proposal appealing" (Ezhilarasan 2018). Therefore, some drugs may serve more than their intended purpose. For example, thalidomide is a pan-kinase inhibitor used in oncology (Iwata, *et al.* 2015), originally used as an antiemetic, and now used to treat multiple myeloma (Kumar, *et al.* 2020).It has a main indication for erectile dysfunction as well as a secondary indication (Fink, *et al.* 2002) and repurposing indications for idiopathic pulmonary hypertension therapy (Barnett and Machado 2006).

Reuse as a potential therapeutic strategy for idiopathic pulmonary hypertension (Arriola Apelo and Lamming 2016). The FDA has noted a decline in the count of medications approved by them since 1995. In light of the fast-paced progress in bioinformatics and the processing of vast biological data, the practice of medication repositioning has gained significant traction in recent times. Medication repositioning significantly reduces the time and cost of medication development. A fresh drug target was found in 1-2 years, but developing a repositioned treatment required an average of 8 years(Arriola Apelo, *et al.* 2016). Furthermore, the R&D costs for pharmaceutical repositioning are lower than those for traditional approaches. Due to medication repositioning, several countries have addressed cost obstacles. Instead of spending $12 billion on a conventional approach, they would spend $1.6 billion using a drug repositioning methodology to create a new medication (Fontana, *et al.* 2016). Therefore, this process is less expensive, quicker, and riskier than conventional drug development (Xue, *et al.* 2018). Due to a number of successful reintroductions and various indications, repositioning has emerged as a viable alternative in a number of medical specialties. For instance, aspirin has a variety of uses, from short-term therapeutic uses to extended preventative uses (Jourdan, *et al.* 2020; Moffat, *et al.* 2017).

Many drugs on the market currently have previously unknown or off-target effects and might be used safely for cancer prevention and treatment. These ancient medications were repurposed in oncology as adjuvants and were eventually discovered to help cancer patients (Zhang, *et al.* 2021b). Oncology has also benefited from drug repurposing. Phase 1 clinical trials for cancer drugs are thought to provide approval in 5% of cases (Barradell and Fitton 1995). In addition, 2,5-dimethyl celecoxib and OSU-03012, two

Table 1. Treatment of different stages in CRC

Stages of CRC	Treatment Modalities	5-year survival rate	ref
Stage 1	Endoscopic or surgical excision of the pedunculated malignant polyp and surrounding lymph nodes.	~ 90%	(Bujanda, *et al.* 2010)
Stage 2	Surgery, in isolation, deemphasizes the necessity of adjuvant chemotherapy unless there are notable high-risk attributes evident.	~ 75%	(Rebuzzi, *et al.* 2020)
Stage 3	Adjuvant chemotherapy in addition to surgery.	~ 60%	(Rebuzzi, *et al.* 2020)
Stage 4	The therapies available include chemotherapy, tailored therapy, immunotherapy, surgery, radiation, ablation, and stenting.	~ 3%	(Krasteva and Georgieva 2022)

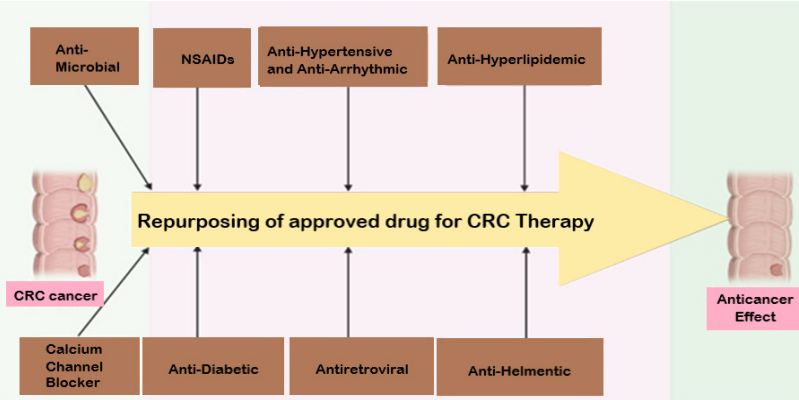

Figure 1. Approved drugs repurposed for colorectal cancer therapy

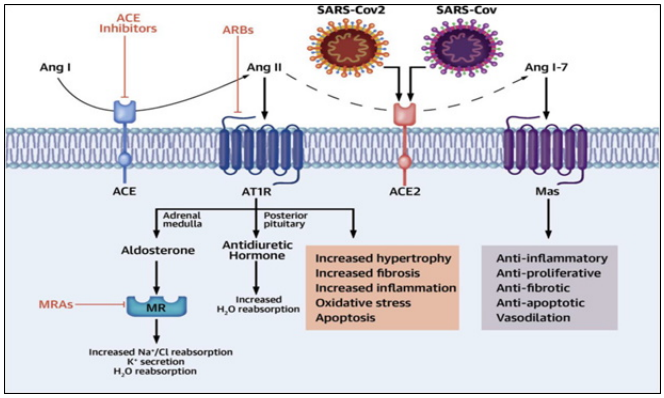

Figure 2. Pathway showing action of ACEI, ARBs and MRAs.

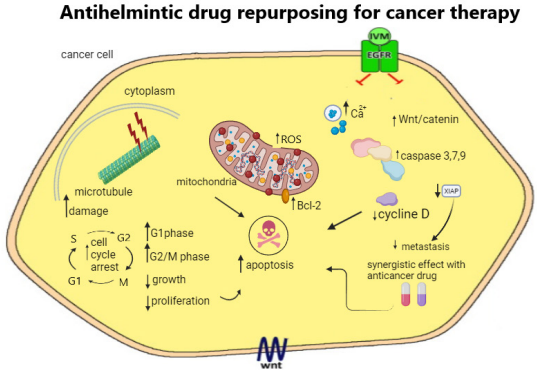

Figure 3. An illustrative diagram displaying the pertinent mechanisms of utilizing anthelmintic drugs in cancer treatment is presented. Symbolically, an increase is denoted by ↑, while a decrease is denoted by ↓. The diagram includes the representation of various components such as Bcl-2 (B-cell lymphoma 2), ROS (reactive oxygen species), Wnt (Wingless-related integration site), and XIAP (X-linked inhibitor of apoptosis protein).

celecoxib derivatives, have been developed and proposed for the therapy of viruses (most recently SARS-CoV-2), inflammation, metabolism, and cancer progression. These molecules may be promising anticancer molecules as they exhibit more potent antitumor properties than celecoxib. These old drugs are being repurposed in oncology, added as adjuvants, and ultimately found to benefit cancer patients (Xie, *et al.* 2021). The stability of cancer cell filopodia is decreased by several calcium channel blockers, such as felodipine and amlodipine besylate, which inhibits the growth, invasion, and dissemination of cancer cells (Benfield, *et al.* 1986). Other terms for drug repositioning include drug redirection, drug profiling, drug diversion, drug redistribution, and treatment switching (Jarada, *et al.* 2020). After an accidental finding, the advantages of altering drugs locations became clear, triggering a rise in interest in predictive techniques for outcome optimization (Benfield, *et al.* 1986). A popular area of study right now is alternative cancer treatment drugs (Berkovic, *et al.* 2021). Numerous methods fall within the category of experimental or computational models (Berkovic, *et al.* 2021; Bernshteyn, *et al.* 2022). The former approach commonly utilizes integrated *in vitro/in vivo* models employing chemical libraries for the examination of binding, or *in vitro* evaluation of contact affinity and stability, also referred to as binding assays. Alterations in cellular lineage contribute to the emergence of phenotypic patterns. Phenotypic approaches use libraries of well-known compounds to examine and characterize cellular responses in an effort to simulate disease in experimental cellular environments (Bernshteyn, *et al.* 2022). In silico models based on structure-based principles were also used to analyze known compounds. Medication-oriented methodologies explore potential alternative applications by leveraging existing medication knowledge, including insights from pharmacodynamics, biochemistry, side effect characteristics, and genetic information. The potential for pharmaceutical repurposing are defined by knowledge-based approaches, which use well-characterized molecular disease pathways (Berkovic, *et al.* 2021). Big data computing techniques evolve in lockstep with the availability of gene and disease datasets. Utilizing data mining, machine learning, and network analysis, computational drug repositioning collects massive datasets pertaining to transcriptomic, proteomics, therapeutic efficacy, response, and even modifiable disease-specific clinical values (Berkovic, *et al.* 2021). This information clarifies intricate biological processes, such as the regulation of epigenetic changes in cancer cells. Additionally, drug redirection techniques can be used to modify the epigenetics of cancer cells and increase susceptibility through differential transcriptional expression. According to one study, 45 FDA-approved medications function in conjunction with histone deacetylase inhibitors and methylation inhibitors. The effects of 85 FDA-approved drugs that specifically focus on these drug categories and their influence on the positive reactions of colon cancer cells are also assessed by the writers. In summary, our findings shed light on the advantages and hurdles associated with the strategy of medication repositioning in creating tailored and exceptionally efficient treatment protocols, which incorporate previously unidentified drug interactions (Raynal, *et al.* 2017). **Figure 1** depict the list of approved drugs which have been repurposed for CRC therapy with promising effect.

Nonsteroidal Anti-Inflammatory Drugs

Moreover, several research studies indicate that the prolonged utilization of low-dose aspirin diminishes the likelihood of developing colorectal cancer and adenoma (Schjerning, *et al.* 2020). By inhibiting the enzyme cyclooxygenase (COX), NSAIDs can exert anti-inflammatory, analgesic, and antipyretic effects (Bacchi, *et al.* 2012). NSAIDs, frequently used as pain relievers, are a commonly employed type of medication for inflammation that is not of a hormonal nature (Sheng, *et al.* 2020). Aspirin's influence on colorectal carcinogenesis involves several pathways (Grancher, *et al.* 2018). Aspirin blocks platelet hobby this is related to most cancers metastasis and immune evasion (Kopp, *et al.* 2009). In addition, numerous research investigations suggest that the extended use of small amounts of aspirin reduces the chances of developing colorectal cancer and adenoma (Chan, *et al.* 2007; Drew, *et al.* 2016; Grancher, *et al.* 2018). Celecoxib acts by inhibiting COX-2 selectively and reversibly, decreasing inflammation and discomfort without altering platelets (McAdam, *et al.* 1999). Several investigations have indicated that celecoxib enhances CRC cell radiosensitivity (Dulai, *et al.* 2016; Xu, *et al.* 2017).

In over 40 observational studies, nonsteroidal anti-inflammatory drugs (NSAIDs) appear to reduce colorectal adenoma, colorectal cancer incidence, and colorectal cancer mortality (Hawk and Levin 2005). COX-2 (cyclooxygenase) is found in adenomas but not in normal intestinal mucosa. COX-2 stimulates the manufacture of prostaglandin E2 (PGE2) in epithelial tissues, activating signaling pathways that promote cell growth and prevent cell death (Pai, *et al.* 2002; Tsujii and DuBois 1995). Initially developed to address pain and inflammation, Celecoxib and other specific COX-2 inhibitors also exhibit anticancer capabilities when administered to patients afflicted with familial adenomatous polyposis (Steinbach, *et al.* 2000). In a nutshell, Monica *et alet alet al.* discovered that taking celecoxib in adults at high risk for colorectal cancer reduced the frequency of patients with documented adenomas significantly in a three-year experiment (Bertagnolli, *et al.* 2006).

Anti-Hypertensives and Anti-Arrhythmic Drugs

ACEIs and ARBs have the potential to not just decrease blood pressure, but also possess unique properties that shield the heart **Figure 2** (Maione, *et al.* 2011). It is not, however, confined to hypertension and heart failure (Hradec 2018). Kubota *et alet alet al.* conducted an *in vivo* research and found that ACE inhibitors and

ARBs would reduce colitis-induced CRC in obese mice by reducing chronic inflammation and oxidative stress (Kubota, *et al.* 2011). Other studies have found that people on RAS inhibitors have a lower risk of colorectal cancer, polyp development, and distant metastases (Childers 2015; Kedika, *et al.* 2011). Beta-blockers are commonly used compounds that inhibit adrenergic receptors (AR) triggered by endogenous catecholamines. AR signaling appears to be critical for cancer formation and metastasis, as well as tumor growth, invasion, migration, angiogenesis, apoptosis, and anonymity (Chang, *et al.* 2015; Lutgendorf, *et al.* 2003). Propranolol is a beta-blocker that affects the cardiovascular system in a nonselective manner. Propranolol hydrochloride, an antihypertensive drug, is administered to manage conditions such as hypertension, pheochromocytoma, myocardial infarction, arrhythmia, anginal attack, and hypertrophic cardiomyopathy. Furthermore, it is utilized to alleviate symptoms of sympathetic overactivity in hyperthyroidism, anxiety disorders, and tremors (Al-Majed, *et al.* 2017). In addition, the growth of colorectal cancer in tumors is halted by propranolol, as it triggers the activation of CD8+ T cells within the body and hinders the functioning of the AKT/MAPK pathway (Liao, *et al.* 2020). Ping-Ying Chang *et alet alet al.* discovered that propranolol reduces the risk of colorectal cancer (Chang, *et al.* 2015). More than half a century has passed since the first β-blocker, propranolol, was developed for medical use. Since the discovery of next-generation beta-blockers such as nebivolol, the search for new compounds has continued, and may include substances known to have potentially enhanced beta-blocking properties (Ogrodowczyk, *et al.* 2016).

Researchers have discovered that the abnormal function of calcium channels plays a crucial role in the progression and formation of tumors, as it reduces the activation of transcription factors that promote the growth and dissemination of colorectal cancer (CRC). Moreover, aside from revitalizing supervisors, Nifedipine (NIFE) also reduces the levels of programmed death ligand 1 (PD-L1) within CRC cells and PD-1 in CD8+ T cells. The effectiveness of immune checkpoint blockade treatment in CRC may be enhanced by utilizing NIFE as a promising therapeutic approach (Berkovic, *et al.* 2021; Grancher, *et al.* 2022). Catecholamines and its receptors, notably those in the -AR families, play critical roles in normal physiological function via -adrenergic receptors (-ARs). The fight-or-flight response in the body is regulated by the -adrenergic pathway, which is under the control of the sympathetic nervous system (Bertagnolli, *et al.* 2006). -AR signaling appears to be important for cancer development and metastasis, controlling tumor growth, invasion, migration, angiogenesis, apoptosis, and anoikic. (Cole and Sood 2012; Sood, *et al.* 2010; Sood, *et al.* 2006; Thaker, *et al.* 2006).

Anti-Hyperlipidemic Drugs

Statins not only reduce cholesterol and decrease cardiovascular risk, but they also have independent pleura-stimulating actions. Their potential as alternative cancer therapies has drawn a lot of interest, with statins' anticancer properties being one among them (Hecht, *et al.* 2013). Statins, a class of pharmaceuticals with multifaceted uses including combating cancer, impede the vital enzyme known as 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase. This particular enzyme governs the conversion of HMG-CoA into mevalonate (Fluge, *et al.* 2009), Overseeing the crucial stage of the liver's cholesterol creation process. A substantial reduction in the likelihood of developing CRC has been associated with the long-term use of statins, as revealed by extensive research involving over 2000 participants, indicating an odds ratio of 0.50 and a confidence interval of 95% (Dickerman, *et al.* 2020; Poynter, *et al.* 2005). Statins provided very little protection against the emergence of CRC, according to a significant meta-analysis that included 31 studies and more than 1.6 million patients (Chimenti, *et al.* 2018; Cole and Sood 2012). For individuals with CRC, repositioning this medication may have therapeutic benefits.

Anti-Diabetic Drugs

Metformin is a medication that is taken orally and is commonly prescribed for the management of type-2 diabetes. As a biguanide compound, it improves the body's sensitivity to insulin, reduces the absorption of glucose in the intestines, and lowers the production of glucose in the liver (Buse, *et al.* 2020). Metformin stands as the initial choice in medications when treating type-2 diabetes, and it is commonly prescribed worldwide for this ailment, either on its own or in conjunction with insulin and other hypoglycemic treatments (Flory and Lipska 2019). Metformin has been proven in previous research to have a preventive impact on CRC risk and prognosis (Berkovic, *et al.* 2021; Cunha Júnior, *et al.* 2021; Ng, *et al.* 2020). Recent research indicates that metformin obstructs the mTOR pathway, a vital component in the enhancement and propagation of CRC cells (Benson, *et al.* 2017). Metformin also decreases the activation of the insulin-like growth factor (IGF) receptor and the growth of colorectal tumors by lowering insulin and insulin growth factors (Hradec 2018; Yang, *et al.* 2017) using AMP-activated protein kinase as a target (Benson, *et al.* 2017),(Chatterjee and Bivona 2019). Metformin has been shown in previous studies to promote apoptosis in nuclear factor-B (NF-B) cell lines through modifying oxidative stress and inflammatory responses (Nguyen, *et al.* 2019; Saber, *et al.* 2016). Metformin may also make cancer cell lines more sensitive to chemotherapeutic drugs including 5-fluorouracil, irinotecan, and Paclitaxel (Khader, *et al.* 2021; Kim, *et al.* 2017; Rocha, *et al.* 2011). Metformin, a first-line therapy for type-2 diabetes, appears to be a potential chemo preventive agent for malignancies, including CRC (Berkovic, *et al.* 2021).

Certain drugs such as dapagliflozin, empagliflozin, and tofogliflozin have been proven effective in reducing glucose levels in people with

type-2 diabetes through clinical trials. The mechanism of action for these medications involves the inhibition of glucose reabsorption in the kidneys via a specific sodium-glucose co-transporter-2 (SGLT2). The drug dapagliflozin specifically alters the behavior of CRC cells by influencing their connections with collagen types I and IV through the activation of ADAM10. As a result, the complete DDR1 is compromised (Okada, *et al.* 2020). Dapagliflozin hindered the proliferation of colon cells in the human colon cancer cell line HCT116 by enhancing the activation of Erk (Saito, *et al.* 2015). Okada *et alet alet al.* presented a case study where the combination of SGLT2 inhibition and the EGFR inhibitor cetuximab showed promising results in curtailing tumor growth and decreasing CEA levels in colorectal cancer patients with liver metastases (Okada, *et al.* 2018).These findings point to a potentially unique role for Dapagliflozin as an anticancer drug in tumor cell populations that lack UGT1A9 (Saito, *et al.* 2015).

Antiretroviral drugs

The risk of pharmacokinetic interactions is substantial in HIV-infected cancer patients undergoing a combination of highly active antiretroviral therapy (HAART) and systemic anticancer therapy (Loulergue, *et al.* 2017). Antiviral medications called nucleoside analogues are frequently administered for treating viral infections such as HIV, HBV, HCV, CMV, HSV, and VZV (2012b).

Telomerase is a reverse transcriptase that is responsible for the creation of telomeric DNA repeats from scratch. In cancer therapy, blocking this enzyme, which is essential for tumor formation and progression, is a promising therapeutic strategy (Jafri, *et al.* 2016; Sanford, *et al.* 2020). The treatment of HIV has shown positive and well-tolerated outcomes over an extended period using two prodrug variants, Tenofovir disoproxil fumarate (TDF) and Tenofovir alafenamide (TAF) (Moorthy, *et al.* 2020). Tenofovir obstructs the activity of reverse transcriptase, an enzyme, and functions as an antiviral nucleoside (Wassner, *et al.* 2020). Tenofovir, in human beings, also inhibits the functioning of telomerase (Hu, *et al.* 2015). Sheriff and colleagues discovered that administering tenofovir to rats at a rate of 50 mg/kg over a period of 24 weeks resulted in reduced cell growth in the colon, which can be attributed to the reduced levels of Bcl-2 and cyclin D1 expression (Hukezalie, *et al.* 2012).

The potential repurposing of Zidovudine, a licensed drug for HIV treatment, is currently under investigation due to its unexplored antibacterial properties (Antonello, *et al.* 2021). Zidovudine, also referred to as azidothymidine, is a medication utilized to address the infection caused by the human immunodeficiency virus (HIV), functioning as an inhibitor of reverse transcriptase activity by targeting nucleosides (Kinloch-De Loës, *et al.* 1995). Zidovudine was found by Brown *et alet alet al.* to hinder the activity of telomerase in the HT-29 colon cancer cell line (Brown, *et al.* 2003). Additionally, it was found by Fang and colleagues that the effectiveness of zidovudine in suppressing cancer growth in colon cells was influenced by its ability to enhance the expression of the p53 Puma/Bax/Noxa pathway. This pathway is responsible for promoting programmed cell death, leading to the suggestion that activating the p53 Puma/Bax/Noxa pathway results in halting the cell cycle (Fang, *et al.* 2017).

Protease inhibitors (PIs) are medications that impede the function of HIV protease in order to suppress viral generation, infection, and replication (Hellinger and Gruber 2019).Indinavir and saquinavir are PIs that inhibit angiogenesis and matrix metalloproteinases, limiting tumor cell proliferation and reducing tumor invasion and progression (Toschi, *et al.* 2011). Mule *et alet alet al.* also observed that ritonavir, when combined with butyrate, causes apoptosis in CRC cells (Mühl, *et al.* 2004).According to research, it also inhibits cytochrome P450-3A4. Ritonavir is now being researched for usage in the treatment of several forms of cancer due to its mode of action (Talha and Dhamoon 2022; Vermunt, *et al.* 2021). Ritonavir's anti-tumor actions are most likely due to proteolysis inhibition, which results in p21 accumulation (Gaedicke, *et al.* 2002), reduced TNF-, IL-6, IL-8, and VEGF production (Burlaka, *et al.* 2018). The findings indicate that ritonavir's effectiveness in treating tumors may be tied to its ability to selectively disrupt proteasomal proteolysis. *In vitro* and *in vivo* experiments demonstrate that rotogravure, an essential inhibitor, effectively inhibits the invasion of colorectal tumor cells that are dependent on Fascin-1 (Alburquerque-González, *et al.* 2021) (Table 2). The presence of Fascin-1, a protein that connects actin fibers, is linked to enhanced outcomes in individuals with CRC, while also indicating a negative prognosis, heightened chances of recurrence, and reduced survival rates (Shi, *et al.* 2020; Tampakis, *et al.* 2021).

Anti-Helminthic Drugs

Mebendazole, a well-known medication for eliminating parasites, is commonly prescribed for the treatment of various types of roundworms, such as pinworms and hookworms, as well as tapeworms and other parasitic infections (Juneja, *et al.* 2017b; Kannen, *et al.* 2020). Mebendazole, a versatile benzimidazole compound, hinders the formation of tubulin polymers, leading to a decrease in the production of microtubules (Lacey 1990). Several CRC cell lines, including HCT-116, RKO, HT-29, HT-8, and SW626, are cytotoxic to mebendazole (Laudisi, *et al.* 2020; Nygren, *et al.* 2013). Nygren and Larsson discovered that mebendazole showed positive results in treating metastatic lesions in patients with resistant metastatic CRCI. In a separate study, the effectiveness of mebendazole was assessed on five colon cancer cell lines and three non-malignant colonic epithelial cell lines, revealing promising targeted anti-tumor effects (Nygren, *et al.* 2013). A different examination conducted on mice that have constant APC gene mutations revealed that the conjunction of mebendazole and sulindac (a nonsteroidal anti-inflammatory drug) lessened the

Table 2. Medications that have been reimagined for utilization in treating colorectal cancer.

Drug	Pharmaceutical category	Original Indication	Possible Mode(s) of Action	Effect(s)	Reference
Butyrate	Anti-Retroviral Drugs	Probiotic	The inhibition of miR-92a	Colon cancer cell growth is slowed.	(Hu, *et al.* 2015)
Sirolimus	Other	Prevention of kidney transplant rejection	Inhibition of EMT, caused by the deletion of FBXW7, is impeded due to the induction of DR5, which is dependent on CHOP, when 4E-BP1 is dephosphorylated	Apoptosis Reduced angiogenesis colon cancer cell growth and invasion are inhibited	(He, *et al.* 2016; Mussin, *et al.* 2017; Wang, *et al.* 2013)
Fluoxetine	Other	Antidepressant	Activation of NF-B and IKK phosphorylation is inhibited, resulting in cell-cycle arrest at G0/G1	Suppressed tumorigenesis associated with colitis Dysplasia and angiogenesis are suppressed	(Kannen, *et al.* 2012a; Koh, *et al.* 2011)
Valproate	Other	Antipsychotic	HDAC-mediated transcriptional repression is alleviated by histone hyperacetylation	Decreased viability Increased cytotoxicity	(Patel and Patel 2018)
Mefloquine	Anti-Microbials	Antimalarial	NF-B activation inhibition	Apoptosis Growth halt	(Xu, *et al.* 2018)
Artesunate		Antimalarial	β-catenin undergoes a decrease in expression levels	Apoptosis Cytotoxicity	(Kumar, *et al.* 2019; Verma, *et al.* 2017)
Gemifloxacin		Antibiotic	TNF-, IL-6, IL-8, and VEGF are being suppressed.	Restriction of cell movement and penetration occurs.	(Kan, *et al.* 2013)
Azithromycin		Antibiotic	Upregulation of p62 and LC-3B inhibits autophagy	Apoptosis	(Qiao, *et al.* 2018; Tanaka, *et al.* 2020; Toriyama, *et al.* 2021)
Clarithromycin		Antibiotic	Autophagy inhibition by hERG1 targeting	Angiogenesis is inhibited. Colon cancer cell proliferation is slowed	(Carella, *et al.* 2012; Petroni, *et al.* 2020; Schafranek, *et al.* 2013; Yatsunami, *et al.* 1997)
Doxycycline		Antibiotic	The suppression of matrix metalloproteinase activity, Provoking the activation of caspases-3, -8, and -9 resulting in the release of cytochrome c and redistribution of Bax	Apoptosis hampers cellular proliferation and possesses the capacity to infiltrate tissues	(Onoda, *et al.* 2004; Onoda, *et al.* 2006)
Raltegravir	Anti-Retroviral Drugs	anti-HIV drug	Facin-1 inhibition	Suppressed invasion	(Alburquerque-González, *et al.* 2021)
Saquinavir		Anti-HIV drug	Proteasomes and matrix metalloproteinases are involved in preventing the growth of blood vessels, and they hinder the breakdown of p21, causing its accumulation	Apoptosis Suppressed growth	(Pajonk, *et al.* 2002; Toschi, *et al.* 2011)
Ritonavir	Anti-Helminthic Drugs	Anti-HIV drug	Proteolytic degradation inhibition and p21 accumulation Reduced TNF-, IL-6, IL-8, and VEGF production heme oxygenase-1 expression has increased	Apoptosis Suppressed angiogenesis	(Gaedicke, *et al.* 2002; Mühl, *et al.* 2004; Pati, *et al.* 2002)
Indinavir	Anti-Retroviral Drugs	Anti-HIV drug	Prevention of blood vessel growth in a manner unrelated to proteasome activity or matrix metalloproteinases	Suppressed growth	(Toschi, *et al.* 2011)
Efavirenz	Anti-Retroviral Drugs	Anti-HIV drug	Phosphorylation of p53 is activated	Cytotoxicity against several colon cancer cell lines	(Hecht, *et al.* 2013)
Zidovudine	Anti-Retroviral Drugs	Anti-HIV drug	P53-Puma/Bax/Noxa pathway exhibits heightened expression	Cell cycle arrest Apoptosis	(Brown, *et al.* 2003; Fang, *et al.* 2017)
Tenofovir	Anti-Retroviral Drugs	anti-HIV drug	The p53-p21 pathway is turned on.	Proliferation, oxidative stress, and inflammation inhibition	(Sherif, *et al.* 2021)
Niclosamide	Anti-Helminthic Drugs	Anti-Helminthic Drugs	Facin-1 inhibition	Proliferation was reduced in several human CRC cell lines.	(Osada, *et al.* 2011; Sack, *et al.* 2011)
Mebendazole	Anti-Helminthic Drugs	Anti-Helminthic Drugs	MYC1 inhibition	Cytotoxic activity against different colon cancer cell lines	(Nygren, *et al.* 2013; Williamson, *et al.* 2016)

Table 2. *(continued)*

Dapagliflozin	Anti-Diabetic Drugs	Antihyperglycemic	The effect of collagen types I and IV on cellular contact Erk phosphorylation has increased.	Colon cancer cell adhesion and proliferation are reduced.	(Okada, *et al.* 2020; Saito, *et al.* 2015)
Metformin	Anti-Diabetic Drugs	Antihyperglycemic	mTOR inhibition Inflammatory responses to oxidative stress and nuclear factor-B are modulated.	CRC cell lines undergo apoptosis	(Nguyen, *et al.* 2019; Saber, *et al.* 2016; Slattery, *et al.* 2010; Vial, *et al.* 2019; Zi, *et al.* 2018)
Lovastatin	Anti-Hyperlipidemic Drugs	Antilipidemic	Inhibition of MACC1	Cancer development and metastatic formation were slowed.	(Juneja, *et al.* 2017a; Qi, *et al.* 2021)
Celecoxib	Nonsteroidal Anti-Inflammatory Drugs	Anti-inflammatory	Effect on p53 via COX-2-independent regulation of p21 and CyclinD1 expression BCCIP upregulation Radiosensitivity in the HCT116 cell line	Decreased viability Increased cytotoxicity	(Bertagnolli, *et al.* 2006; Xu, *et al.* 2017)
Aspirin	Nonsteroidal Anti-Inflammatory Drugs	Antiplatelet	COX-2 inhibition, inhibition of the c-MYC transcriptional activation, and antiplatelet mode of action	The occurrence of cancer metastasis and immune evasion has been greatly reduced	(Chan, *et al.* 2007; Dovizio, *et al.* 2012; Kopp, *et al.* 2009; Thun, *et al.* 2012)
Nebivolol	Anti-Hypertensives and Anti-Arrhythmic Drugs	Hypertension and other indications	Inhibiting mitochondrial respiration occurs as a result of reducing the activity of Complex I in the respiratory chain	Suppressed the growth of colon cancer cells	(Nuevo-Tapioles, *et al.* 2020)
ACEIs/ARBs	**	Hypertension	There has been a reduction in chronic inflammation and oxidative stress	Adenomatous colon polyps are less likely to form	(Kedika, *et al.* 2011; Kubota, *et al.* 2011)
Propranolol	Noncardioselective β-blocker	Hypertension	Frequently recommended for the treatment of ailments such as high blood pressure, tumor in the adrenal gland, heart attack, irregular heartbeat, and chest pain	Suppressed tumor growth reduced phosphorylation of AKT/MAPK pathways, Activated Autologous CD8 + T Cells	(Al-Majed, *et al.* 2017; Liao, *et al.* 2020)
Nifedipine	Calcium Channel Blocker	Hypertension	Used to treat angina, acute bouts of hypertension, moderate to severe hypertension (alone or in combination), and Raynaud's phenomenon.	Suppressed Progression, decreased expression PD-L1	(Sorkin, *et al.* 1985; Wu, *et al.* 2020)
Morphine	Opioid receptor agonist	Sedation, euphoria and analgesia	Agonist of the μ and k receptors	AKT-MTOR and RAS-MAPK pathways were activated, which boosted proliferation, migration, and invasion while also promoting resistance to EGFR inhibitors.	(Lu, *et al.* 2021; Pacifici 2016)
Ciprofloxacin	Anti-Microbials	Antibiotic	Inhibited of bacterial DNA gyrase	Anti-proliferative, G2/M cell cycle arrest, and apoptosis	(Alaaeldin, *et al.* 2020; Campoli-Richards, *et al.* 1988)
Penicillin	Anti-Microbials	Antibiotic	Bacteriostatic or bactericidal agent	Disrupted mitochondrial function and energy metabolism, inhibited growth and metastasis.	(Hobby, *et al.* 1942; Hu, *et al.* 2021)
Pantoprazole	Antacid	Proton-pump inhibitor	Used to treat esophagitis caused by gastroesophageal reflux disease and pathological hyper secretory disorders such as Zollinger-Ellison syndrome	Inhibited growth by inhibiting T-cell-derived protein kinase	(Bernshteyn and Masood 2022; Zeng, *et al.* 2016)
Metronidazole	Anti-Microbials	Antibiotic	Metronidazole indirectly inhibits DNA synthesis and repair of existing DNA.	Reduced proliferation, and overall tumor growth	(Bullman, *et al.* 2017; Dingsdag and Hunter 2018)
Dexamethasone	Anti-inflammatory corticosteroid	Anti-inflammatory	Relieved inflammation (swelling, heat, redness, and pain)	Inhibited significant tumor	(Lammers, *et al.* 2020; Ma, *et al.* 2020)
Propranolol	β-Blockers	Anti-Arrhythmic		Reduced proliferation, and overall tumor growth, β-AR-blocker	(Chang, *et al.* 2015; Hicks, *et al.* 2013)
Pyrvinium pamoate		Anthelmintic drug		Cell growth, migration, and AKT protein expression were all suppressed.	(Zheng, *et al.* 2021)

quantity and magnitude of minuscule creatures. It impacts the functioning of the intestines by disturbing the MYC and COX-2 routes, alongside hindering the formation of blood vessels and the generation of cytokines that foster tumor growth (Williamson, *et al.* 2016). Mebendazole has been found to preferentially promote cancer cell death by traditional apoptosis and cell cycle arrest processes involving microtubule instability (Petersen and Baird 2021).

Niclosamide (NCL) is an anthelmintic medication with systemic anti-inflammatory and antiviral properties that is widely utilized in the treatment of a variety of disorders (Figure 3). In human biological processes, NCL modulates oxidative phosphorylation and the segregation of numerous signaling pathways (Al-Kuraishy, *et al.* 2021). Niclosamide is a salicylamide analog that affects multiple signaling pathways via uncoupled oxidative phosphorylation (Chen, *et al.* 2018). In APC-mutant CRC, we discovered that Axin2, a genuine canonical Wnt target gene, works as an activator of aYAP phosphorylation(Kang, *et al.* 2021). Nicodamid inhibits the Wnt/-catenin signaling pathway, which is hyperactive in 80% of people with sporadic CRC (Kannen, *et al.* 2012b). HCT-116, Caco2, and HT-29 are three human CRC cell lines that have been studied *in vitro* and *in vivo*. These cell lines show lower proliferation, which may be caused by enhanced autophagy (Kang, *et al.* 2021). Additionally, Kang *et alet alet al.* discovered that by inhibiting Wnt and YAP (Kan, *et al.* 2013), niclosamide in conjunction with metformin could reduce her APC-mutated CRC. This finding shows that niclosamide administration using MNPs with increased branching polymer activity might be an useful technique for treating colorectal cancer (Ahmad, *et al.* 2020). Pyrvinium pamoate (PP) has been intensively explored as an anthelmintic in cancer therapy throughout the last decade (Momtazi-Borojeni, *et al.* 2018). PP has been shown to inhibit cancer cell growth and survival during glucose deprivation (Esumi, *et al.* 2004). Wnt signaling, on the other hand, promotes CRC start and development by altering hummingbird adenomatous polyposis (APC) and –catenin (Novellasdemunt, *et al.* 2015). PP has been demonstrated to inhibit PI3K-dependent signaling pathways by efficiently blocking downstream PI3K targets such as AKT and P70S6K (Carrella, *et al.* 2016). Colorectal cancer has been proven to be suppressed by PP (CRC) (Zheng, *et al.* 2021). Furthermore, low molecular weight PPs can limit CRC cell movement (Zheng, *et al.* 2021). In addition, Fang and his team uncovered a startling fact that the effectiveness of zidovudine for combating colon cancer cells is attributed to the enhancement of the p53 Puma/Bax/Noxa pathway, a biological mechanism that promotes the demise of cells. This discovery suggests that the initiation of the p53 Puma/Bax/Noxa pathway results in the cessation of cellular replication (Momtazi-Borojeni, *et al.* 2018).

Anti-Microbials

The discovery of novel anticancer drugs based on existing antibiotics in recent years has opened up new therapeutic avenues for a variety of cancer types. (Markowska, *et al.* 2019). Other antibacterial medicines, such as Doxycycline, a semi-synthetic antibiotic derived from tetracycline that is used to treat a variety of diseases, have being investigated for repurposing to treat colon cancer (Cunha, *et al.* 1982). Furthermore, studies have demonstrated the ability of doxycycline to hinder the activity of metalloproteinases, on the other hand, clarithromycin has proven to be a potent suppressor of angiogenesis (El Zarif, *et al.* 2022). Clarithromycin is an effective angiogenesis inhibitor (Yatsunami, *et al.* 1997). It has been demonstrated to be more effective when combined with authorized anticancer medicines (Carella, *et al.* 2012; Komatsu, *et al.* 2013; Schafranek, *et al.* 2013). It has also been linked to autophagy deficiency in myeloma cells (Nakamura, *et al.* 2010). Autophagy inhibition is regarded to be a viable treatment approach for colon cancer (Burada, *et al.* 2015; Mokarram, *et al.* 2017). A study carried out by Petroni *et alet alet al.* found that by focusing on hERG1, clarithromycin can effectively regulate autophagy in cells of human CRC and reduce the growth of tumors (Petroni, *et al.* 2020). The data suggests that clarithromycin has strong potential to inhibit tumor-induced angiogenesis. It works by decreasing the growth of endothelial cell tubules, thereby making it a promising candidate for therapeutic use in tablet form (Yatsunami, *et al.* 1997).

Azithromycin (a macrolide antibiotic) is created by inserting a methyl-substituted nitrogen atom into the lactone ring at number 15, act by blocking protein synthesis to limit the bacterial growth and inhibits autophagy as an anticancer mechanism (Booth, *et al.* 2018; Brenner, *et al.* 2014). When combined with substances that activate tumor necrosis factor-associated cell death (TRAIL), azithromycin exhibits an enhanced anticancer effect in colon cancer cells. Chao *et al.* reported that azithromycin can hinder autophagy by modifying the levels of p62 and LC-3B, resulting in the death of colon cancer cells (Qiao, *et al.* 2018).

Gemifloxacin (GMF) is a fourth-generation Fluoroquinolone antibiotic that is taken orally and is used to treat mild to severe respiratory infections caused by susceptible organisms (2012a). Clarithromycin is another antibiotic with potential cancer therapy (Zhanel, *et al.* 2006). Gemifloxacin was found to impede the movement and infiltration of SW620 and LoVol colon cancer cells. Moreover, it regulated snail expression to restrict the creation of epithelial-mesenchymal junctions (EMT) (Kan, *et al.* 2013). Hence, there is a possibility that GMF could serve as a fresh therapeutic substance to counteract the spread of colon cancer (Kan, *et al.* 2013).

Antimalarial medicines are also being investigated for their potential use in the treatment of colon cancer (El Zarif, *et al.* 2022).

Artesunate is an antimalarial medicine used to prevent persons with moderate Plasmodium falciparum malaria (Barradell and Fitton 1995). Artesunate, a water-soluble artemisinin hemisuccinate derivative, possesses anti-inflammatory, anticancer, and immunomodulatory properties (Kong, *et al.* 2019). In studies conducted on preclinical CRC models, it has been observed that artesunate is effective in reducing inflammation and oxidative stress (Kumar, *et al.* 2019). According to Eiffel and his team, Artesunate has the ability to destroy cancer cells using two different methods: either by relying on the presence of the p53 protein or by operating independently of it (Efferth, *et al.* 2003) implicated in -catenin negative regulation (Verma, *et al.* 2017). Mefloquine, some other antimalarial medication, has been proven in mice to affect to the NF-B tumor signaling system and induce growth arrest and death of CRC cells (Xu, *et al.* 2018). The data given here clearly demonstrate that the afore mentioned antibiotics should be recognized as new medicines capable of eradicating cancer cells and cancer stem cells in the near future (CSCs) (Markowska, *et al.* 2019). Metronidazole (MND) has a narrow range of action that includes different protozoa as well as the majority of Gram-negative and Gram-positive anaerobes. Metronidazole is efficient against protozoa such *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis*, which were the first successful therapies licensed(Freeman, *et al.* 1997). MND, according to Zaim Baldakji and colleagues, reduces the therapeutic index in the treatment of colorectal cancer by altering the clearance of 5-fluorouracil (5-FU) (Bardakji, *et al.* 1986). Also, giving the MND to animals with colon cancer xenografts decreased Fusobacterium bacterial load, cancer cell proliferation, and total tumor development (Bullman, *et al.* 2017).

Penicillin is a well-known and extensively used antibiotic that is both safe and effective (Bertolini, *et al.* 2015). It is indicated for the treatment of pharyngitis, scarlet fever, hemolytic *streptococcal cellulitis*, *pneumococcal pneumonia*, otitis media, meningitis, tetanus, and clostridial gangrene (Dalal, *et al.* 2017). Few research have looked at the use of antibiotics in tumor therapy (Kee, *et al.* 2018; Suehiro, *et al.* 2018). As per study, mitochondria not only produce and supply energy, but they also participate in a number of physiological and pathological processes (Abate, *et al.* 2020; Bock and Tait 2020; Vidali, *et al.* 2015). Mitochondrial dysfunction can result in a variety of pathological alterations, such as: B (Inflammation, oxidative stress response, as well as apoptosis). Alterations in mitochondria induced by structural and functional abnormalities, such as B. Cellular respiratory chain enzyme dysfunction, altered membrane potential and permeability, calcium ion excess, and pro-apoptotic protein overexpression are all major ways of suppressing cell growth and finally leading to apoptosis (Pistritto, *et al.* 2016). Higher mitochondrial outer membrane permeability and membrane potential are related with increased cytochrome c release (Gogvadze, *et al.* 2015). Available research suggests that CRC cell growth and mitochondrial dysfunction are implicated (Akagi and Baba 2019; Burlaka, *et al.* 2018; Lawrie, *et al.* 2018). Disruption of mitochondrial energy metabolism promotes membrane permeability, cytochrome c release into the cytoplasm, and apoptotic agent release, finally leading to cellular death (Chimenti, *et al.* 2018). Penicillin, in conclusion, works by inhibiting growth and metastasis in colorectal cancer cells via influencing mitochondrial activity and energy use (Hu, *et al.* 2021).These findings and studies call for more research into antibiotic intervention as a viable therapy for colorectal cancer patients.

Other Drugs

Neuropathy medications are increasingly being evaluated as therapy alternatives for cancer patients and are started immediately after diagnosis (Kumar, *et al.* 2020; Verma, *et al.* 2019). Valproic acid (VPA) was initially synthesized in 1882, but its anticonvulsant characteristics were not recognized until the early 1960 (Rissardo, *et al.* 2021). Friedman and co., has been demonstrated to reduce adenocarcinoma cell survival in a dose-dependent manner, especially when Valproic acid coupled with mitomycin C (Friedmann, *et al.* 2006). Furthermore, Moroni *et alet alet al.* discovered that valproate increased the cytotoxicity of bosutinib in colon cancer cells (Mologni, *et al.* 2009). Sodium valproate exhibits notable cytotoxic effects at concentrations of 2 and 4 mM/mL. Administration of sodium valproate results in an upsurge of intracellular ROS production. Additionally, this treatment induces mitochondrial disruption, cellular aging, structural harm, and alteration in E-cadherin expression specifically in HT-29 cells (Anirudh and Ezhilarasan 2021). This might be explained by boosting H3 and H4 histone hyperacetylation, which improves anti-tumor action and alleviates transcriptional inhibition by HDACs (Göttlicher, *et al.* 2001; Patel and Patel 2018). Overall, sodium valproate has the potential to be repurposed in colon cancer. Serotonin appears to have both proliferative and carcinogenic effects on colorectal cancers, according to experimental research (Lee, *et al.* 2017). Fluoxetine belongs to a class of drugs called selective serotonin reuptake inhibitors (SSRIs) and is used to treat depression (Benfield, *et al.* 1986). Fluoxetine was found to hinder the activation of NF-B and decreased the phosphorylation of IB kinase (IKK) and IB in mice with colitis-associated colon cancer. This ultimately led to the suppression of DSS-induced colitis and colitis-related tumors. These findings were reported by Kannen *et alet alet al.* Apart from its suppressive effects on colitis, the antiproliferative effects of fluoxetine on HT29 colon cancer cells were also explored. It was discovered that fluoxetine increased the percentage of HT29 cells in the G0/G1 phase of the cell cycle and boosted the expression of p27 protein. Additionally, fluoxetine demonstrated the ability to decrease the

occurrence of dysplasia and angiogenesis-related dysplasia in colonic tissue. Moreover, there was a noticeable reduction in the number of angiogenic cells, especially within CD133, CD34, and CD31-positive cell clusters (Kannen, *et al*. 2012a).

Rapamycin (sirolimus) is a macrolide immunosuppressant and blocks the molecular specificity of the rapamycin (mTOR) protein kinase and enhances lifespan in model species like as mice (Arriola Apelo and Lamming 2016). Rapamycin is an FDA-approved mTOR inhibitor intended to reduce kidney transplant rejection (Sehgal 2003). In both laboratory settings and living organisms, it has been proven that the growth of colon tumors can be reduced by the use of sirolimus and metformin together (Mussin, *et al*. 2017). In colon cancer cells, it was demonstrated that mTOR inhibitors facilitate programmed cell death by decreasing the phosphorylation of 4E-BP1 through CHOP-dependent DR5. As a consequence, there is a decrease in tumor growth, angiogenesis, and invasion (He, *et al*. 2016). Furthermore, Sirolimus has been found to reduce FBXW7 loss-driven EMT via its mTOR inhibitory effect, reducing CRC cell migration and invasion (Mussin, *et al*. 2017).

Probiotics are live microorganisms which have been shown to boost human health. They include bacteria and yeast (Kim, *et al*. 2019). Researchers are currently studying probiotics as a potential treatment for CRC. Hu *et alet alet al*. found that the growth of miR-92a in human CRC cells was suppressed by butyrate (Hu, *et al*. 2015). Butyrate has been discovered as a main product of gut microbial fermentation, a critical modulator of gut microbiota control in whole-body energy balance (Zhang, *et al*. 2021a). Butyrate, when combined with Ritonavir, can cause apoptosis in DLD-1 colon cancer cells (Mühl, *et al*. 2004).These compounds' optimum dosages and specificities have been found, and they are being utilized in conjunction with conventional cancer treatments to give an inexpensive, safe, and efficient method to overcoming drug resistance and extending patient life (Mezheyeuski, *et al*. 2016).

Dexamethasone (DEX), an over-the-counter medication used to treat a variety of inflammatory illnesses, can effectively inhibit the production of inflammatory chemicals (Ma, *et al*. 2020). In laboratory experiments and living organisms, DEX has been discovered to inhibit the expansion of cancer cells (Wu, *et al*. 2019; Yano, *et al*. 2006). High doses of DEX have demonstrated their effectiveness in diminishing tumor size, obstructing vascular infiltration, and decreasing the presence of cellular growth indicators like Ki67 and c-Myc, along with the anti-cell death marker Bcl2 (Xu, *et al*. 2020). The results suggest that a complex mechanism is responsible for the effective inhibition of tumor growth by high-dose DEX. This mechanism includes activating M1-like TAMs and disrupting the absorption and utilization of glucose and lipids, thus reducing the availability of vital nutrients and energy for cancer cells. Furthermore, it was discovered that high-dose DEX effectively hinders cell proliferation. Additionally, the activation of M1-like TAMs and the impairment of glucose and lipid metabolism also contribute to the suppression of tumor cell proliferation and encouragement of cell death. These noteworthy findings propose the potential use of high-dose DEX as an adjunct treatment in combination with chemotherapy or immunotherapy for patients with advanced cancer (Xu, *et al*. 2020).

Pantoprazole, which falls under the category of proton pump inhibitors (PPIs), is frequently employed within medical facilities. The approval from the FDA for the usage of pantoprazole extends to the management of various conditions, encompassing erosive esophagitis attributable to gastroesophageal reflux disease, as well as pathological hypersecretion syndromes like Zollinger-Ellison syndrome (Bernshteyn and Masood 2022). Researchers Xiaoyu Zenget *et alet alet al*. have proven that pantoprazole, an inhibitor of TOPK, a protein kinase derived from T-cells, can effectively impede the growth of colon cancer cells both in laboratory settings and in living organisms. This discovery highlights the significance of targeting TOPK in therapeutic interventions against tumors, as it plays a vital role in the development and advancement of cancer(Zeng, *et al*. 2016).

Morphine seems to be an analgesic that acts as an agonist of and k receptors. Morphine-like agonists generate analgesia, drowsiness, euphoria, and respiratory depression via acting on opioid receptors (Pacifici 2016). Frequently employed in cancer treatment, targeted molecular therapy impedes cancer cell proliferation by directing attention to vital biological targets essential for tumor development and the initiation of malignant circumstances (Kovacs, *et al*. 2015). Patients with advanced colorectal cancer (CRC) frequently indicate the occurrence of intense pain, which necessitates the utilization of opioid medications (Sekandarzad, *et al*. 2017). According to studies, opioids could potentially enhance tumor proliferation and the emergence of resistance against cancer-fighting medications. This phenomenon may potentially deteriorate the outlook for cancer patients (Lennon, *et al*. 2014; Maher, *et al*. 2019; Singleton, *et al*. 2015). The impact of morphine on EGFR (epidermal growth factor receptor) activation through MOR was witnessed. This leads to the stimulation of AKT-MTOR and RAS-MAPK signaling pathways, resulting in the promotion of proliferation, migration, and invasion of CRC cell lines. Additionally, it also increases resistance against EGFR inhibitors (Lu, *et al*. 2021). Overall, morphine-EGFR signaling appears to be a viable therapeutic target for individuals with CRC.

Nifedipine (NIFE), listed as an essential medication by the World Health Organization (WHO), functions as an effective and safe L-type dihydropyridine calcium channel blocker. It successfully inhibits the influx of Ca2+ and is suitable for various types of hypertension. Consequently, in clinical investigations, NIFE is often prioritized as the initial choice for long-term antihypertensive

Table 3. Status of clinical trials of different FDA-approved drugs intended to be repurposed for CRC treatment.

Intervention/ Treatment	Status	Phase	Clinical Trial Number	Patient Population	Patients Enrolled	Primary Outcome Measures	Secondary Outcome Measures	REF
Aspirin	Active, not recruiting	3	NCT02467582	Stages II and III PIK3CA-mutated CRC previously treated with surgery	185	DFS after 6 years	It's time to repeat. OS Cancer-related survival Unfavorable outcomes	(Gray, *et al.* 2018)
Aspirin	Recruiting	3	NCT02301286	Stages II and III CRC	1588	OS	DFS TTF	(Frouws, *et al.* 2017)
Aspirin	Recruiting	3	NCT03464305	Stages II and III CRC	400	5-year OS	DFS TTF	(Ittaman, *et al.* 2014)
Aspirin	Recruiting	3	NCT02945033	*PI3K*-mutated CRC	246	whatever comes first: recurrence, second CRC, or death	5-year OS Adverse events	(Lin, *et al.* 2020)
Aspirin	Active, not recruiting	3	NCT00565708	Dukes C and high-risk Dukes B CRCs	1587	DFS	OS	(Ali, *et al.* 2011)
Nivolumab + Ipilimumab with or without Celecoxib	Recruiting	2	NCT03026140	Stages I to III CRC	60	The occurrence of unfavorable events	Immunotherapy's ability to activate the immune system Survival without a relapse	(Verschoor, *et al.* 2022)
Folfox + bevacizumab with or without mebendazole	Recruiting	3	NCT03925662	Stage IV CRC	40	ORR	-	(Hegazy, *et al.* 2022)
Metformin	Recruiting	2	NCT03359681	CRC	48	Ki67 expression on tumor samples	Immunoscore Immunological alterations in blood samples with cleaved caspase-3 expression Cell proliferation *in vitro*	(Kamarudin, *et al.* 2019)
Axitinib + hydroxychloroquine	Recruiting	1	NCT04873895	Liver-dominant metastatic CRC	25	Serious adverse events	ORR in the presence of liver metastases PFS OS	(El Zarif, *et al.* 2022)
Neratinib + valproate	Recruiting	1/2	NCT03919292	Advanced solid tumors including CRC	113	Recommended phase 2 dose	Unfavorable outcomes Antitumor properties PFS	(Booth, *et al.* 2018)

medication. The origins of NIFE's potential in fighting cancer can be linked to a lancet publication from 2001, which presented a case study. (Yang and Friedlander 2001). Lastly, Ling Wu *et alet alet al.* demonstrate that NIFE reduces PD-L1 expression in tumor cells while increasing PD-1 expression in T lymphocytes, thereby imitating and enhancing the action of PD-1/PD-L1 inhibitors in cancer (Wu, *et al.* 2020).

Toxicological Study:

Utilizing drugs for novel therapeutic purposes presents a promising approach in tackling therapy resistance in colon cancer. This strategy effectively addresses obstacles such as comorbidities, diminished chemotherapy toxicity, and drug resistance. One study has demonstrated the advantageous nature of repurposing drugs in treating colorectal cancer, as it not only addresses underlying conditions but also minimizes chemotherapy toxicity (El Zarif, *et al.* 2022). Additional research emphasizes the significance of traditional chemotherapy and targeted therapy for colon cancer, while proposing that the repurposing of drugs could aid in overcoming resistance (Fong and To 2019). Moreover, various categories of repurposed medications exist, including those that were initially perceived as toxic but have proven to be safe for alternative applications. This comprehensive perspective sheds light on the realm of drug repurposing in cancer treatment (Nowak-Sliwinska, *et al.* 2019). Another recent study examines the overall impact of drug repurposing in CRC treatment, emphasizing the importance of evaluating survival rates, toxicity levels, and side effects to gauge the effectiveness of this approach (El Zarif, *et al.* 2022). Additionally, the investigation of combining repurposed drugs reveals strategies for achieving enhanced effectiveness, surpassing drug resistance, and minimizing toxicity in CRC (Duarte and Vale 2022). Repurposing existing drugs also emerges as a promising solution in combating multidrug-resistant cancers by effectively addressing the obstacles intertwined with resistance in cancer therapy (Dinić, *et al.* 2020).

Clinical Trials on Drug Repurposing in Colon Cancer:

Several ongoing clinical trials on the repurposed drugs to be used in CRC have been reported till now. Some of them are in the very initial stages of their clinical trials while others have successfully passed the initial scrutiny and made it to the next phase of the trial. The details of such drugs have been documented in **Table 3.** A study was conducted to examine the effects of Aspirin (80 mg daily) as an additional treatment for patients with stage II or III PIK3CA-mutated colon cancer. The results of the study demonstrated that Aspirin, when compared to a placebo, displayed greater effectiveness in reducing the likelihood of cancer recurrence and enhancing survival rates. This was supported by two equivalent phase 3 clinical trials, registered as NCT02301286 and NCT03464305, as documented on ClinicalTrials.gov (NCT02467582). The findings of the third phase of the ASCOLT clinical trial suggest that individuals diagnosed with Dukes C CRC and who consumed a daily dose of 200 mg aspirin for a duration of three years experienced a survival rate of both disease-free and overall well-being after five years (ClinicalTrials.gov; NCT00565708). Contrarily, the ASPIK study conducted in France compared the effects of a placebo to a daily intake of 100 mg aspirin on the likelihood of local or distant recurrence, the development of another CRC, or mortality from any cause (ClinicalTrials.gov; NCT02945033). The therapeutic goals of the NICHE phase-2 clinical trial involve the utilization of Celecoxib, Nivolumab, and Ipilimumab in the neoadjuvant setting for participants diagnosed with stage I to III colon cancer. Currently, in a phase 3 clinical trial registered on ClinicalTrials.gov as NCT03925662, there is ongoing research on the possible inclusion of Mebendazole, an anti-helminthic drug, in combination with FOLFOX and Bevacizumab for patients diagnosed with stage IV CRC. MECORA is a new stage of clinical research that aims to analyze the efficacy of metformin in people who do not have diabetes but are suffering from non-diabetic colon cancer (ClinicalTrials.gov; NCT03359681). The objective of the clinical trial in phase IB is to evaluate the safety of using antimalarial hydroxychloroquine along with Axitinib and hepatic chemoembolization (ClinicalTrials.gov; NCT04873895). Additionally, there is ongoing phase 1/2 clinical research that aims to examine the safety and dosage of neratinib + sodium valproate in individuals with high-risk malignancies, specifically RAS-mutated CRC patients (ClinicalTrials.gov; NCT03919292).

Conclusion and Perspective

The research in oncology is achieving a new height with each passing day. Research across the globe is working day and night to develop new techniques and approaches to combat the cause and effect of cancers. Although there are various forms of cancers and each form has its lethal effect, CRC (Colorectal cancer) has pulled the attention of the scientific community due to its aggressive nature. With context to its malignancy, it ranks 2nd after the lung cancer in the list of malignant tumors globally. Also, CRC accounts for the 3rd highest rate of mortality among all the forms of cancer listed till date, with marginal survival rates in many age-groups. Additionally, the latest data indicates that there will be a near exponential surge in the new cases of CRC in coming decades. Although, several conventional treatment approaches using the application of chemotherapeutic drugs, radiological treatment and surgical intervention has been used for CRC treatment but side effects of such therapies and development of drug resistance have raised serious questions over the success rate of such interventions.

Therefore, the need for new anticancer therapies using some new anticancer drug is an urgent necessity. But, the discovery of a brand-new drug is a very long journey, involving huge amount of

resources including cost, time, manpower, regulatory hurdles, administrative procedures, and bureaucratic checkpoints that causes delay in the approval process of these drugs, so that they will be available in the market for clinical application. According to a statistical report out of the total anticancer drugs that enter the clinical trials, only about 5% get approval of FDA. Exploiting the idea of repurposing, these established drugs have been investigated to exploit the possibility of using them in anticancer therapy. The art of drug repurposing has gained popularity since these molecules have well-established pharmacokinetics and pharmacodynamic profiles. Also, such therapies are considered safe since the Toxicity data of these drugs have already been generated and passed the test for safety to be administered in humans. Hence, the above effort has paved way for an accelerated and economical way to identify new therapeutic targets by just simply performing efficacy studies of these drugs to get regulatory approval.

The need for fresh methods to treat cancer leads to a change in focus towards reusing already available drugs. The scientific community acknowledges the long process of creating completely new medications and embraces the idea of repurposing existing ones. This method not only speeds up the identification of therapeutic targets but also guarantees safety through well-established knowledge of how these drugs are processed and how they affect the body. Although there is hope in using existing drugs for the treatment of CRC, it is vital to consider the outlook of research in this area. It is essential to thoroughly investigate new targets for therapy and thoroughly evaluate the survival rates and potential side effects of repurposed drugs. Despite the limited success of current research, it is evident that continuous exploration is necessary to attain the utmost advantages for patients suffering from CRC. The purpose of using repurposed drugs for CRC management is to target them to the newly developed targets of the cancer progression, so that some new therapies could be developed to counter their progression and provide relief to the patients. Also, with the development of artificial intelligence and various computational tools aided by the application of Big Data, identification of new targets and mapping of binding sites by integrating them with clinical database has made it possible to use the repurposed drugs as anticancer agents. Although, such efforts of drug repurposing still need to be evaluated for the rate of survival and possible toxicities. The research on this subject is still at its very early stage with a very limited rate of success, but still in-depth investigation and research need to be performed to extract the maximum benefit of such ideas in the patients suffering from CRC. Some of the drugs like Butyrate, Sirolimus, Fluoxetine, Valproate, Mefloquine, Artesunate, Gemifloxacin, Doxycycline, Raltegravir, Indinavir, Efavirenz, Zidovudine, Niclosamide, Dapagliflozin, Lovastatin, Celecoxib, Morphine, Penicillin, Dexamethasone and Pyrvinium pamoate have been mentioned in this review, but other categories of drug could be a potential candidate as anticancer agent and inhibit the growth of CRC.

Author contribution

M.D., A.M.C., M.F., Z.I., M.A.M., M.A., E.T.A.B. conceptualized, reviewed, edited and wrote the article. All authors read and approved the article before publication.

Acknowledgment

None declared.

Competing financial interests

The authors have no conflict of interest.

Abbreviations

Adrenergic receptors (-ARs), preneoplastic lesions (polyps), cyclooxygenase (COX), prostaglandin E2 (PGE2), 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA),insulin-like growth factor (IGF), sodium-glucose co-transporter-2 (SGLT2), highly active antiretroviral therapy (HAART), Tenofovir disoproxil fumarate (TDF),Tenofovir alafenamide (TAF), Angiotensin-Converting Enzyme Inhibitors (ACEIs) , Angiotensin II Receptor Antagonists (ARBs),Epithelial-mesenchymal junctions (EMT), Valproic acid (VPA),Histone deacetylases (HDACs) ,Selective serotonin reuptake inhibitors (SSRIs).

References

Ahmad, A., Gupta, A., Ansari, M. M., Vyawahare, A., Jayamurugan, G., & Khan, R. (2019). Hyperbranched polymer-functionalized magnetic nanoparticle-mediated hyperthermia and niclosamide bimodal therapy of colorectal cancer cells. ACS Biomaterials Science & Engineering, 6(2), 1102-1111.

Ahmad, J., Garg, A., Mustafa, G., Ahmad, M. Z., Aslam, M., & Mishra, A. (2023). Hybrid Quantum Dot as Promising Tools for Theranostic Application in Cancer. Electronics, 12(4), 972.

Ahmad, M. Z., Ahmad, J., Aslam, M., Khan, M. A., Alasmary, M. Y., & Abdel-Wahab, B. A. (2021). Repurposed drug against COVID-19: nanomedicine as an approach for finding new hope in old medicines. Nano Express, 2(2), 022007.

Akagi, J., & Baba, H. (2019). Hydrogen gas restores exhausted CD8+ T cells in patients with advanced colorectal cancer to improve prognosis. Oncology reports, 41(1), 301-311.

Alaaeldin, R., Nazmy, M. H., Abdel-Aziz, M., Abuo-Rahma, G. E. D. A., & Fathy, M. (2020). Cell Cycle Arrest and Apoptotic Effect of 7-(4-(N-substituted carbamoylmethyl) piperazin-1-yl) Ciprofloxacin-derivative on HCT 116 and A549 Cancer Cells. Anticancer research, 40(5), 2739-2749.

Alburquerque-González, B., Bernabé-García, Á., Bernabé-García, M., Ruiz-Sanz, J., López-Calderón, F. F., Gonnelli, L., ... & Conesa-Zamora, P. (2021). The FDA-approved antiviral raltegravir inhibits fascin1-dependent invasion of colorectal tumor cells in vitro and in vivo. Cancers, 13(4), 861.

Ali, R., Toh, H. C., Chia, W. K., & ASCOLT Trial Investigators. (2011). The utility of Aspirin in Dukes C and High Risk Dukes B Colorectal cancer-The ASCOLT study: Study Protocol for a randomized controlled trial. Trials, 12, 1-8.

Al-Kuraishy, H. M., Al-Gareeb, A. I., Alzahrani, K. J., Alexiou, A., & Batiha, G. E. S. (2021). Niclosamide for Covid-19: bridging the gap. Molecular Biology Reports, 1-8.

Al-Majed, A. A., Bakheit, A. H. H., Abdel Aziz, H. A., Alajmi, F. M., & AlRabiah, H. (2017). Propranolol. Profiles Drug Subst Excip Relat Methodol 42: 287–338.

Anirudh, B. V. M., & Ezhilarasan, D. (2021). Reactive Oxygen Species–Mediated Mitochondrial Dysfunction Triggers Sodium Valproate–Induced Cytotoxicity in Human Colorectal Adenocarcinoma Cells. Journal of Gastrointestinal Cancer, 52, 899-906.

Antonello, R. M., Di Bella, S., Betts, J., La Ragione, R., Bressan, R., Principe, L., ... & Lagatolla, C. (2021). Zidovudine in synergistic combination with fosfomycin: an in vitro and in vivo evaluation against multidrug-resistant Enterobacterales. International journal of antimicrobial agents, 58(1), 106362.

Arriola Apelo, S. I., & Lamming, D. W. (2016). Rapamycin: an InhibiTOR of aging emerges from the soil of Easter Island. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 71(7), 841-849.

Bacchi, S., Palumbo, P., Sponta, A., & Coppolino, M. F. (2012). Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents), 11(1), 52-64.

Bardakji, Z., Jolivet, J., Langelier, Y., Besner, J. G., & Ayoub, J. (1986). 5-Fluorouracil-metronidazole combination therapy in metastatic colorectal cancer: clinical, pharmacokinetic and in vitro cytotoxicity studies. Cancer chemotherapy and pharmacology, 18, 140-144.

Barnett, C. F., & Machado, R. F. (2006). Sildenafil in the treatment of pulmonary hypertension. Vascular health and risk management, 2(4), 411-422.

Barradell, L. B., & Fitton, A. (1995). Artesunate: a review of its pharmacology and therapeutic efficacy in the treatment of malaria. Drugs, 50, 714-741.

Benfield, P., Heel, R. C., & Lewis, S. P. (1986). Fluoxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs, 32, 481-508.

Benson, A. B., Venook, A. P., Cederquist, L., Chan, E., Chen, Y. J., Cooper, H. S., ... & Freedman-Cass, D. (2017). Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 15(3), 370-398.

Berkovic, M. C., Mikulic, D., Bilic-Curcic, I., & Mrzljak, A. (2021). How far along are we in revealing the connection between metformin and colorectal cancer?. World journal of gastroenterology, 27(14), 1362.

Bernshteyn, M. A., & Masood, U. (2023). Pantoprazole.[Updated 2022 Jul 12]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Bertagnolli, M. M., Eagle, C. J., Zauber, A. G., Redston, M., Solomon, S. D., Kim, K., ... & Hawk, E. T. (2006). Celecoxib for the prevention of sporadic colorectal adenomas. New England Journal of Medicine, 355(9), 873-884.

Bertolini, F., Sukhatme, V. P., & Bouche, G. (2015). Drug repurposing in oncology—patient and health systems opportunities. Nature reviews Clinical oncology, 12(12), 732-742.

Bock, F. J., & Tait, S. W. (2020). Mitochondria as multifaceted regulators of cell death. Nature reviews Molecular cell biology, 21(2), 85-100.

Booth, L., Roberts, J. L., Rais, R., Kirkwood, J., Avogadri-Connors, F., Cutler Jr, R. E., ... & Dent, P. (2018). [Neratinib+ Valproate] exposure permanently reduces ERBB1 and RAS expression in 4T1 mammary tumors and enhances M1 macrophage infiltration. Oncotarget, 9(5), 6062.

Brenner, H., & Kloor, M. (2014). Pox cP. colorectal cancer. Lancet, 383(9927), 1490-1502.

Brown, T., Sigurdson, E., Rogatko, A., & Broccoli, D. (2003). Telomerase inhibition using azidothymidine in the HT-29 colon cancer cell line. Annals of surgical oncology, 10, 910-915.

Bujanda, L., Cosme, A., Gil, I., & Arenas-Mirave, J. I. (2010). Malignant colorectal polyps. World journal of gastroenterology: WJG, 16(25), 3103.

Bullman, S., Pedamallu, C. S., Sicinska, E., Clancy, T. E., Zhang, X., Cai, D., ... & Meyerson, M. (2017). Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science, 358(6369), 1443-1448.

Burada, F., Nicoli, E. R., Ciurea, M. E., Uscatu, D. C., Ioana, M., & Gheonea, D. I. (2015). Autophagy in colorectal cancer: An important switch from physiology to pathology. World journal of gastrointestinal oncology, 7(11), 271.

Burlaka, A. P., Ganusevich, I. I., Vovk, A. V., Burlaka, A. A., Gafurov, M. R., & Lukin, S. N. (2018). Colorectal cancer and mitochondrial dysfunctions of the adjunct adipose tissues: a case study. BioMed research international, 2018.

Buse, J. B., Wexler, D. J., Tsapas, A., Rossing, P., Mingrone, G., Mathieu, C., ... & Davies, M. J. (2020). 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care, 43(2), 487-493.

Campoli-Richards, D. M., Monk, J. P., Price, A., Benfield, P., Todd, P. A., & Ward, A. (1988). Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs, 35, 373-447.

Carella, A. M., Beltrami, G., Pica, G., Carella, A., & Catania, G. (2012). Clarithromycin potentiates tyrosine kinase inhibitor treatment in patients with resistant chronic myeloid leukemia. Leukemia & lymphoma, 53(7), 1409-1411.

Carrella, D., Manni, I., Tumaini, B., Dattilo, R., Papaccio, F., Mutarelli, M., ... & Cardone, L. (2016). Computational drugs repositioning identifies inhibitors of oncogenic PI3K/AKT/P70S6K-dependent pathways among FDA-approved compounds. Oncotarget, 7(37), 58743.

Chan, A. T., Ogino, S., & Fuchs, C. S. (2007). Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. New England Journal of Medicine, 356(21), 2131-2142.

Chang, P. Y., Huang, W. Y., Lin, C. L., Huang, T. C., Wu, Y. Y., Chen, J. H., & Kao, C. H. (2015). Propranolol reduces cancer risk: a population-based cohort study. Medicine, 94(27), e1097.

Chatterjee, N., & Bivona, T. G. (2019). Polytherapy and targeted cancer drug resistance. Trends in cancer, 5(3), 170-182.

Chen, W., Mook Jr, R. A., Premont, R. T., & Wang, J. (2018). Niclosamide: Beyond an antihelminthic drug. Cellular signalling, 41, 89-96.

Childers, W. K. (2015). Interactions of the renin-angiotensin system in colorectal cancer and metastasis. International Journal of Colorectal Disease, 30(6), 749-752.

Chimenti, M. S., Sunzini, F., Fiorucci, L., Botti, E., Fonti, G. L., Conigliaro, P., ... & Giunta, A. (2018). Potential role of cytochrome c and tryptase in psoriasis and psoriatic arthritis pathogenesis: focus on resistance to apoptosis and oxidative stress. Frontiers in immunology, 9, 387495.

Cole, S. W., & Sood, A. K. (2012). Molecular pathways: beta-adrenergic signaling in cancer. Clinical cancer research, 18(5), 1201-1206.

Cunha, B. A., Sibley, C. M., & Ristuccia, A. M. (1982). Doxycycline. Therapeutic drug monitoring, 4(2), 115.

Dalal, A., Eskin-Schwartz, M., Mimouni, D., Ray, S., Days, W., Hodak, E., ... & Paul, M. (2017). Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database of Systematic Reviews, (6).

Dekker, E., Tanis, P. J., Vleugels, J. L., Kasi, P. M., & Wallace, M. (2019). Pure-amc. Lancet, 394, 1467-80.

Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2020). Emulating a target trial in case-control designs: an application to statins and colorectal cancer. International journal of epidemiology, 49(5), 1637-1646.

Dingsdag, S. A., & Hunter, N. (2018). Metronidazole: an update on metabolism, structure–cytotoxicity and resistance mechanisms. Journal of Antimicrobial Chemotherapy, 73(2), 265-279.

Dinić, J., Efferth, T., García-Sosa, A. T., Grahovac, J., Padrón, J. M., Pajeva, I., ... & Tsakovska, I. (2020). Repurposing old drugs to fight multidrug resistant cancers. Drug Resistance Updates, 52, 100713.

Dovizio, M., Tacconelli, S., Sostres, C., Ricciotti, E., & Patrignani, P. (2012). Mechanistic and pharmacological issues of aspirin as an anticancer agent. Pharmaceuticals, 5(12), 1346-1371.

Drew, D. A., Cao, Y., & Chan, A. T. (2016). Aspirin and colorectal cancer: the promise of precision chemoprevention. Nature Reviews Cancer, 16(3), 173-186.

Duarte, D., & Vale, N. (2022). Combining repurposed drugs to treat colorectal cancer. Drug Discovery Today, 27(1), 165-184.

Dulai, P. S., Singh, S., Marquez, E., Khera, R., Prokop, L. J., Limburg, P. J., ... & Murad, M. H. (2016). Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. Bmj, 355.

Efferth, T., Sauerbrey, A., Olbrich, A., Gebhart, E., Rauch, P., Weber, H. O., ... & Funk, J. O. (2003). Molecular modes of action of artesunate in tumor cell lines. Molecular pharmacology, 64(2), 382-394.

El Zarif, T., Yibirin, M., De Oliveira-Gomes, D., Machaalani, M., Nawfal, R., Bittar, G., ... & Bitar, N. (2022). Overcoming therapy resistance in colon cancer by drug repurposing. Cancers, 14(9), 2105.

Esra'a, I. K., Ismail, W. W., Mhaidat, N. M., & Alqudah, M. A. (2021). Effect of metformin on irinotecan-induced cell cycle arrest in colorectal cancer cell lines HCT116 and SW480. International Journal of Health Sciences, 15(5), 34.

Esumi, H., Lu, J., Kurashima, Y., & Hanaoka, T. (2004). Antitumor activity of pyrvinium pamoate, 6-(dimethylamino)-2-[2-(2, 5-dimethyl-1-phenyl-1H-pyrrol-3-yl) ethenyl]-1-methyl-quinolinium pamoate salt, showing preferential cytotoxicity during glucose starvation. Cancer science, 95(8), 685-690.

Ezhilarasan, D. (2018). Herbal therapy for cancer: Clinical and experimental perspectives. In Understanding cancer therapies (pp. 129-166). CRC Press.

Fang, X., Hu, T., Yin, H., Yang, J., Tang, W., Hu, S., & Xu, X. (2017). Differences in telomerase activity and the effects of AZT in aneuploid and euploid cells in colon cancer. International Journal of Oncology, 51(2), 525-532.

Fink, H. A., Mac Donald, R., Rutks, I. R., Nelson, D. B., & Wilt, T. J. (2002). Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. Archives of Internal Medicine, 162(12), 1349-1360.

Flory, J., & Lipska, K. (2019). Metformin in 2019. Jama, 321(19), 1926-1927.

Fluge, Ø., Gravdal, K., Carlsen, E., Vonen, B., Kjellevold, K., Refsum, S., ... & Dahl, O. (2009). Expression of EZH2 and Ki-67 in colorectal cancer and associations with treatment response and prognosis. British journal of cancer, 101(8), 1282-1289.

Fong, W., & To, K. K. (2019). Drug repurposing to overcome resistance to various therapies for colorectal cancer. Cellular and molecular life sciences, 76, 3383-3406.

Fontana, L., Cummings, N. E., Apelo, S. I. A., Neuman, J. C., Kasza, I., Schmidt, B. A., ... & Lamming, D. W. (2016). Decreased consumption of branched-chain amino acids improves metabolic health. Cell reports, 16(2), 520-530.

Freeman, C. D., Klutman, N. E., & Lamp, K. C. (1997). Metronidazole: a therapeutic review and update. Drugs, 54, 679-708.

Friedmann, I., Atmaca, A., Chow, K. U., Jäger, E., & Weidmann, E. (2006). Synergistic effects of valproic acid and mitomycin C in adenocarcinoma cell lines and fresh tumor cells of patients with colon cancer. Journal of chemotherapy, 18(4), 415-420.

Frouws, M. A., Bastiaannet, E., Langley, R. E., Chia, W. K., van Herk-Sukel, M. P. P., Lemmens, V. E. P. P., ... & Liefers, G. J. (2017). Effect of low-dose aspirin use on survival of patients with gastrointestinal malignancies; an observational study. British journal of cancer, 116(3), 405-413.

Gaedicke, S., Firat-Geier, E., Constantiniu, O., Lucchiari-Hartz, M., Freudenberg, M., Galanos, C., & Niedermann, G. (2002). Antitumor effect of the human immunodeficiency virus protease inhibitor ritonavir: induction of tumor-cell apoptosis associated with perturbation of proteasomal proteolysis. Cancer research, 62(23), 6901-6908.

Gogvadze, V., Orrenius, S., & Zhivotovsky, B. (2015). Analysis of mitochondrial dysfunction during cell death. Mitochondrial Medicine: Volume I, Probing Mitochondrial Function, 385-393.

Göttlicher, M., Minucci, S., Zhu, P., Krämer, O. H., Schimpf, A., Giavara, S., ... & Heinzel, T. (2001). Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. The EMBO journal.

Grancher A, Michel P, Di Fiore F, Sefrioui D. Aspirine et cancer colorectal [Aspirin and colorectal cancer]. Bull Cancer. 2018 Feb;105(2):171-180. French. doi: 10.1016/j.bulcan.2017.09.013. Epub 2017 Nov 15. PMID: 29153543.

Grancher, A., Michel, P., Di Fiore, F., & Sefrioui, D. (2022). Colorectal cancer chemoprevention: is aspirin still in the game?. Cancer Biology & Therapy, 23(1), 446-461.

Gray, R. T., Coleman, H. G., Hughes, C., Murray, L. J., & Cardwell, C. R. (2018). Low-dose aspirin use and survival in colorectal cancer: results from a population-based cohort study. BMC cancer, 18, 1-8.

Hassan LEA, Al-Suede FS, Fadul SM, Abdul Majid AMS. (2018). Evaluation of antioxidant, antiangiogenic and antitumor properties of Anogeissus leiocarpus against

colon cancer. Angiotherapy, 1(2), pages 056–066.Abate, M., Festa, A., Falco, M., Lombardi, A., Luce, A., Grimaldi, A.,& Misso, G. (2020, February). Mitochondria as playmakers of apoptosis, autophagy and senescence. In Seminars in cell & developmental biology (Vol. 98, pp. 139-153). Academic Press.

Hawk ET, Levin B. Colorectal cancer prevention. J Clin Oncol. 2005 Jan 10;23(2):378-91. doi: 10.1200/JCO.2005.08.097. PMID: 15637400.

He, K., Zheng, X., Li, M., Zhang, L., & Yu, J. (2016). mTOR inhibitors induce apoptosis in colon cancer cells via CHOP-dependent DR5 induction on 4E-BP1 dephosphorylation. Oncogene, 35(2), 148-157.

Hecht, M., Harrer, T., Büttner, M., Schwegler, M., Erber, S., Fietkau, R., & Distel, L. V. (2013). Cytotoxic effect of efavirenz is selective against cancer cells and associated with the cannabinoid system. Aids, 27(13), 2031-2040.

Hegazy, S. K., El-Azab, G. A., Zakaria, F., Mostafa, M. F., & El-Ghoneimy, R. A. (2022). Mebendazole; from an anti-parasitic drug to a promising candidate for drug repurposing in colorectal cancer. Life Sciences, 299, 120536.

Hellinger, R., & Gruber, C. W. (2019). Peptide-based protease inhibitors from plants. Drug discovery today, 24(9), 1877-1889.

Hicks, B. M., Murray, L. J., Powe, D. G., Hughes, C. M., & Cardwell, C. R. (2013). β-Blocker usage and colorectal cancer mortality: a nested case–control study in the UK Clinical Practice Research Datalink cohort. Annals of oncology, 24(12), 3100-3106.

Hijazi, M. A., Gessner, A., & El-Najjar, N. (2023). Repurposing of chronically used drugs in cancer therapy: a chance to grasp. Cancers, 15(12), 3199.

Hobby, G. L., Meyer, K., & Chaffee, E. (1942). Observations on the Mechanism of Action of Penicillin. Proceedings of the Society for Experimental Biology and Medicine, 50(2), 281-285.

Hradec, J. (2018). Pharmacological therapy for chronic heart failure. Vnitrni Lekarstvi, 64(9), 853-859.

Hu, F., Wu, Y., Liu, C., Zhu, Y., Ye, S., Xi, Y., ... & Bu, S. (2021). Penicillin disrupts mitochondrial function and induces autophagy in colorectal cancer cell lines. Oncology Letters, 22(4), 1-10.

Hu, S., Liu, L., Chang, E. B., Wang, J. Y., & Raufman, J. P. (2015). Butyrate inhibits pro-proliferative miR-92a by diminishing c-Myc-induced miR-17-92a cluster transcription in human colon cancer cells. Molecular cancer, 14, 1-15.

Hukezalie, K. R., Thumati, N. R., Coˆte, H. C., & Wong, J. M. (2012). In vitro and ex vivo inhibition of human telomerase by anti-HIV nucleoside reverse transcriptase inhibitors (NRTIs) but not by non-NRTIs. PLoS One, 7(11), e47505.

Ittaman, S. V., VanWormer, J. J., & Rezkalla, S. H. (2014). The role of aspirin in the prevention of cardiovascular disease. Clinical medicine & research, 12(3-4), 147-154.

Iwata, H., Sawada, R., Mizutani, S., & Yamanishi, Y. (2015). Systematic drug repositioning for a wide range of diseases with integrative analyses of phenotypic and molecular data. Journal of chemical information and modeling, 55(2), 446-459.

Jafri, M. A., Ansari, S. A., Alqahtani, M. H., & Shay, J. W. (2016). Roles of telomeres and telomerase in cancer, and advances in telomerase-targeted therapies. Genome medicine, 8, 1-18.

Jarada, T. N., Rokne, J. G., & Alhajj, R. (2020). A review of computational drug repositioning: strategies, approaches, opportunities, challenges, and directions. Journal of cheminformatics, 12, 1-23.

Jourdan, J. P., Bureau, R., Rochais, C., & Dallemagne, P. (2020). Drug repositioning: a brief overview. Journal of Pharmacy and Pharmacology, 72(9), 1145-1151.

Juneja, M., Kobelt, D., Walther, W., Voss, C., Smith, J., Specker, E., ... & Stein, U. (2017). Statin and rottlerin small-molecule inhibitors restrict colon cancer progression and metastasis via MACC1. PLoS Biology, 15(6), e2000784.

Júnior, A. D. C., Bragagnoli, A. C., Costa, F. O., & Carvalheira, J. B. C. (2021). Repurposing metformin for the treatment of gastrointestinal cancer. World journal of gastroenterology, 27(17), 1883.

Kamarudin, M. N. A., Sarker, M. M. R., Zhou, J. R., & Parhar, I. (2019). Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects. Journal of Experimental & Clinical Cancer Research, 38(1), 491.

Kan, J. Y., Hsu, Y. L., Chen, Y. H., Chen, T. C., Wang, J. Y., & Kuo, P. L. (2013). Gemifloxacin, a fluoroquinolone antimicrobial drug, inhibits migration and invasion of human colon cancer cells. BioMed research international, 2013.

Kang, H. E., Seo, Y., Yun, J. S., Song, S. H., Han, D., Cho, E. S., ... & Kim, T. I. (2021). Metformin and niclosamide synergistically suppress Wnt and YAP in APC-mutated colorectal cancer. Cancers, 13(14), 3437.

Kannen, V., Bader, M., Sakita, J. Y., Uyemura, S. A., & Squire, J. A. (2020). The dual role of serotonin in colorectal cancer. Trends in Endocrinology & Metabolism, 31(8), 611-625.

Kannen, V., Hintzsche, H., Zanette, D. L., Silva Jr, W. A., Garcia, S. B., Waaga-Gasser, A. M., & Stopper, H. (2012). Antiproliferative effects of fluoxetine on colon cancer cells and in a colonic carcinogen mouse model. PLoS One, 7(11), e50043.

Kannen, V., Hintzsche, H., Zanette, D. L., Silva Jr, W. A., Garcia, S. B., Waaga-Gasser, A. M., & Stopper, H. (2012). Antiproliferative effects of fluoxetine on colon cancer cells and in a colonic carcinogen mouse model. PLoS One, 7(11), e50043.

Kedika, R., Patel, M., Sahdala, H. N. P., Mahgoub, A., Cipher, D., & Siddiqui, A. A. (2011). Long-term use of angiotensin converting enzyme inhibitors is associated with decreased incidence of advanced adenomatous colon polyps. Journal of clinical gastroenterology, 45(2), e12-e16.

Kee, J. Y., Han, Y. H., Mun, J. G., Um, J. Y., & Hong, S. H. (2018). Pharmacological effect of prohibited combination pair Panax ginseng and Veratrum nigrum on colorectal metastasis in vitro and in vivo. Journal of Ethnopharmacology, 220, 177-187.

Kim, S. H., Kim, S. C., & Ku, J. L. (2017). Metformin increases chemo-sensitivity via gene downregulation encoding DNA replication proteins in 5-Fu resistant colorectal cancer cells. Oncotarget, 8(34), 56546.

Kim, S. K., Guevarra, R. B., Kim, Y. T., Kwon, J., Kim, H., Cho, J. H., ... & Lee, J. H. (2019). Role of probiotics in human gut microbiome-associated diseases.

Kinloch-de Loës, S., Hirschel, B. J., Hoen, B., Cooper, D. A., Tindall, B., Carr, A., ... & Perrin, L. (1995). A controlled trial of zidovudine in primary human immunodeficiency virus infection. New England Journal of Medicine, 333(7), 408-413.

Koh, S. J., Kim, J. M., Kim, I. K., Kim, N., Jung, H. C., Song, I. S., & Kim, J. S. (2011). Fluoxetine inhibits NF-κB signaling in intestinal epithelial cells and ameliorates experimental colitis and colitis-associated colon cancer in mice. American Journal of Physiology-Gastrointestinal and Liver Physiology, 301(1), G9-G19.

Komatsu, S., Moriya, S., Che, X. F., Yokoyama, T., Kohno, N., & Miyazawa, K. (2013). Combined treatment with SAHA, bortezomib, and clarithromycin for concomitant targeting of aggresome formation and intracellular proteolytic pathways enhances ER stress-mediated cell death in breast cancer cells. Biochemical and biophysical research communications, 437(1), 41-47.

Kong, Z., Liu, R., & Cheng, Y. (2019). Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. Biomedicine & Pharmacotherapy, 109, 2043-2053.

Kopp, H. G., Placke, T., & Salih, H. R. (2009). Platelet-derived transforming growth factor-β down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer research, 69(19), 7775-7783.

Kovacs, E., Zorn, J. A., Huang, Y., Barros, T., & Kuriyan, J. (2015). A structural perspective on the regulation of the epidermal growth factor receptor. Annual review of biochemistry, 84, 739-764.

Krasteva, N., & Georgieva, M. (2022). Promising therapeutic strategies for colorectal cancer treatment based on nanomaterials. Pharmaceutics, 14(6), 1213.

Kubota, M., Shimizu, M., Sakai, H., Yasuda, Y., Ohno, T., Kochi, T., ... & Moriwaki, H. (2011). Renin–angiotensin system inhibitors suppress azoxymethane-induced colonic preneoplastic lesions in C57BL/KsJ-db/db obese mice. Biochemical and biophysical research communications, 410(1), 108-113.

Kumar, S. K., Callander, N. S., Adekola, K., Anderson, L., Baljevic, M., Campagnaro, E., ... & Kumar, R. (2020). Multiple myeloma, version 3.2021, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 18(12), 1685-1717.

Kumar, V. L., Verma, S., & Das, P. (2019). Artesunate suppresses inflammation and oxidative stress in a rat model of colorectal cancer. Drug Development Research, 80(8), 1089-1097.

Lacey, E. (1990). Mode of action of benzimidazoles. Parasitology today, 6(4), 112-115.

Lammers, T., Sofias, A. M., Van der Meel, R., Schiffelers, R., Storm, G., Tacke, F., ... & Metselaar, J. M. (2020). Dexamethasone nanomedicines for COVID-19. Nature nanotechnology, 15(8), 622-624.

Laudisi, F., Marônek, M., Di Grazia, A., Monteleone, G., & Stolfi, C. (2020). Repositioning of anthelmintic drugs for the treatment of cancers of the digestive system. International Journal of Molecular Sciences, 21(14), 4957.

Lawrie, T. A., Green, J. T., Beresford, M., Wedlake, L., Burden, S., Davidson, S. E., ... & Andreyev, H. J. N. (2018). Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews, (1).

Lee, H. C., Chiu, W. C., Wang, T. N., Liao, Y. T., Chien, I. C., Lee, Y., ... & Chen, V. C. H. (2017). Antidepressants and colorectal cancer: A population-based nested case-control study. Journal of Affective Disorders, 207, 353-358.

Lennon, F. E., Mirzapoiazova, T., Mambetsariev, B., Poroyko, V. A., Salgia, R., Moss, J., & Singleton, P. A. (2014). The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. PloS one, 9(3), e91577.

Liao, P., Song, K., Zhu, Z., Liu, Z., Zhang, W., Li, W., ... & He, Y. (2020). Propranolol suppresses the growth of colorectal cancer through simultaneously activating autologous CD8+ T cells and inhibiting tumor AKT/MAPK pathway. Clinical Pharmacology & Therapeutics, 108(3), 606-615.

Lin, J. L., Lin, J. X., Zheng, C. H., Li, P., Xie, J. W., Wang, J. B., ... & Huang, C. M. (2020). Relationship between aspirin use of esophageal, gastric and colorectal cancer patient survival: a meta-analysis. BMC cancer, 20, 1-15.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. PMID: 31643176.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Nucleoside Analogues. [Updated 2020 May 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548938/

Loulergue, P., Merad, M., Coriat, R., Ducreux, M., Planchard, D., Boige, V., ... & Mir, O. (2017). Safety of raltegravir-based antiretroviral therapy in HIV-infected patients receiving multi-kinase inhibitors. Investigational new drugs, 35, 247-249.

Lu, H., Zhang, H., Weng, M. L., Zhang, J., Jiang, N., Cata, J. P., ... & Miao, C. H. (2021). Morphine promotes tumorigenesis and cetuximab resistance via EGFR signaling activation in human colorectal cancer. Journal of Cellular Physiology, 236(6), 4445-4454.

Lutgendorf, S. K., Cole, S., Costanzo, E., Bradley, S., Coffin, J., Jabbari, S., ... & Sood, A. K. (2003). Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. Clinical Cancer Research, 9(12), 4514-4521.

Ma, S., Song, W., Xu, Y., Si, X., Zhang, D., Lv, S., ... & Chen, X. (2020). Neutralizing tumor-promoting inflammation with polypeptide-dexamethasone conjugate for microenvironment modulation and colorectal cancer therapy. Biomaterials, 232, 119676.

Maher, D. P., Walia, D., & Heller, N. M. (2019). Suppression of human natural killer cells by different classes of opioids. Anesthesia & Analgesia, 128(5), 1013-1021.

Maione, A., Navaneethan, S. D., Graziano, G., Mitchell, R., Johnson, D., Mann, J. F., ... & Strippoli, G. F. (2011). Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrology Dialysis Transplantation, 26(9), 2827-2847.

Markowska, A., Kaysiewicz, J., Markowska, J., & Huczyński, A. (2019). Doxycycline, salinomycin, monensin and ivermectin repositioned as cancer drugs. Bioorganic & Medicinal Chemistry Letters, 29(13), 1549-1554.

McAdam, B. F., Catella-Lawson, F., Mardini, I. A., Kapoor, S., Lawson, J. A., & FitzGerald, G. A. (1999). Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proceedings of the National Academy of Sciences, 96(1), 272-277.

Mezheyeuski, A., Hrynchyk, I., Karlberg, M., Portyanko, A., Egevad, L., Ragnhammar, P., ... & Östman, A. (2016). Image analysis-derived metrics of

histomorphological complexity predicts prognosis and treatment response in stage II-III colon cancer. Scientific reports, 6(1), 36149.

Moffat, J. G., Vincent, F., Lee, J. A., Eder, J., & Prunotto, M. (2017). Opportunities and challenges in phenotypic drug discovery: an industry perspective. Nature reviews Drug discovery, 16(8), 531-543.

Mokarram, P., Albokashy, M., Zarghooni, M., Moosavi, M. A., Sepehri, Z., Chen, Q. M., ... & Ghavami, S. (2017). New frontiers in the treatment of colorectal cancer: Autophagy and the unfolded protein response as promising targets. Autophagy, 13(5), 781-819.

Mologni, L., Cleris, L., Magistroni, V., Piazza, R., Boschelli, F., Formelli, F., & Gambacorti-Passerini, C. (2009). Valproic acid enhances bosutinib cytotoxicity in colon cancer cells. International journal of cancer, 124(8), 1990-1996.

Momtazi-borojeni, A. A., Abdollahi, E., Ghasemi, F., Caraglia, M., & Sahebkar, A. (2018). The novel role of pyrvinium in cancer therapy. Journal of cellular physiology, 233(4), 2871-2881.

Moorthy, G. S., Lalley-Chareczko, L., Koenig, H. C., & Zuppa, A. F. (2020). Tenofovir urine assay to monitor adherence to HIV pre-exposure prophylaxis. Current clinical pharmacology, 15(2), 102-104.

Mühl, H., Paulukat, J., Höfler, S., Hellmuth, M., Franzen, R., & Pfeilschifter, J. (2004). The HIV protease inhibitor ritonavir synergizes with butyrate for induction of apoptotic cell death and mediates expression of heme oxygenase-1 in DLD-1 colon carcinoma cells. British journal of pharmacology, 143(7), 890-898.

Mussin, N., Oh, S. C., Lee, K. W., Park, M. Y., Seo, S., Yi, N. J., ... & Suh, K. S. (2017). Sirolimus and metformin synergistically inhibits colon cancer in vitro and in vivo. Journal of Korean Medical Science, 32(9), 1385.

Nakamura, M., Kikukawa, Y., Takeya, M., Mitsuya, H., & Hata, H. (2010). Clarithromycin attenuates autophagy in myeloma cells. International journal of oncology, 37(4), 815-820.

Ng, C. A. W., Jiang, A. A., Toh, E. M. S., Ng, C. H., Ong, Z. H., Peng, S., ... & Khoo, C. M. (2020). Metformin and colorectal cancer: a systematic review, meta-analysis and meta-regression. International journal of colorectal disease, 35, 1501-1512.

Nguyen, T. T., Ung, T. T., Li, S., Lian, S., Xia, Y., Park, S. Y., & Do Jung, Y. (2019). Metformin inhibits lithocholic acid-induced interleukin 8 upregulation in colorectal cancer cells by suppressing ROS production and NF-kB activity. Scientific reports, 9(1), 2003.

Nikolaou, M., Pavlopoulou, A., Georgakilas, A. G., & Kyrodimos, E. (2018). The challenge of drug resistance in cancer treatment: a current overview. Clinical & Experimental Metastasis, 35, 309-318.

Novellasdemunt, L., Antas, P., & Li, V. S. (2015). Targeting Wnt signaling in colorectal cancer. A review in the theme: cell signaling: proteins, pathways and mechanisms. American Journal of Physiology-Cell Physiology, 309(8), C511-C521.

Nowak-Sliwinska, P., Scapozza, L., & i Altaba, A. R. (2019). Drug repurposing in oncology: Compounds, pathways, phenotypes and computational approaches for colorectal cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1871(2), 434-454.

Nuevo-Tapioles, C., Santacatterina, F., Stamatakis, K., Núñez de Arenas, C., Gómez de Cedrón, M., Formentini, L., & Cuezva, J. M. (2020). Coordinate β-adrenergic inhibition of mitochondrial activity and angiogenesis arrest tumor growth. Nature communications, 11(1), 3606.

Nygren, P., Fryknäs, M., Ågerup, B., & Larsson, R. (2013). Repositioning of the anthelmintic drug mebendazole for the treatment for colon cancer. Journal of cancer research and clinical oncology, 139, 2133-2140.

Ogrodowczyk, M., Dettlaff, K., & Jelinska, A. (2016). Beta-blockers: current state of knowledge and perspectives. Mini reviews in medicinal chemistry, 16(1), 40-54.

Okada, J., Matsumoto, S., Kaira, K., Saito, T., Yamada, E., Yokoo, H., ... & Yamada, M. (2018). Sodium glucose cotransporter 2 inhibition combined with cetuximab significantly reduced tumor size and carcinoembryonic antigen level in colon cancer metastatic to liver. Clinical Colorectal Cancer, 17(1), e45-e48.

Okada, J., Yamada, E., Saito, T., Yokoo, H., Osaki, A., Shimoda, Y., ... & Yamada, M. (2020). Dapagliflozin inhibits cell adhesion to collagen I and IV and increases ectodomain proteolytic cleavage of DDR1 by increasing ADAM10 activity. Molecules, 25(3), 495.

Onoda, T., Ono, T., Dhar, D. K., Yamanoi, A., & Nagasue, N. (2006). Tetracycline analogues (doxycycline and COL-3) induce caspase-dependent and-independent apoptosis in human colon cancer cells. International journal of cancer, 118(5), 1309-1315.

Onoda, T., Ono, T., Dhar, D. K., Yamanoi, A., Fujii, T., & Nagasue, N. (2004). Doxycycline inhibits cell proliferation and invasive potential: combination therapy with cyclooxygenase-2 inhibitor in human colorectal cancer cells. Journal of Laboratory and Clinical Medicine, 143(4), 207-216.

Osada, T., Chen, M., Yang, X. Y., Spasojevic, I., Vandeusen, J. B., Hsu, D., ... & Lyerly, H. K. (2011). Antihelminth compound niclosamide downregulates Wnt signaling and elicits antitumor responses in tumors with activating APC mutations. Cancer research, 71(12), 4172-4182.

Pacifici, G. M. (2016). Metabolism and pharmacokinetics of morphine in neonates: A review. Clinics, 71, 474-480.

Pai, R., Soreghan, B., Szabo, I. L., Pavelka, M., Baatar, D., & Tarnawski, A. S. (2002). Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. Nature medicine, 8(3), 289-293.

Pajonk, F., Himmelsbach, J., Riess, K., Sommer, A., & McBride, W. H. (2002). The human immunodeficiency virus (HIV)-1 protease inhibitor saquinavir inhibits proteasome function and causes apoptosis and radiosensitization in non-HIV-associated human cancer cells. Cancer research, 62(18), 5230-5235.

Patel, M. M., & Patel, B. M. (2018). Repurposing of sodium valproate in colon cancer associated with diabetes mellitus: Role of HDAC inhibition. European Journal of Pharmaceutical Sciences, 121, 188-199.

Pati, S., Pelser, C. B., Dufraine, J., Bryant, J. L., Reitz Jr, M. S., & Weichold, F. F. (2002). Antitumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi sarcoma. Blood, The Journal of the American Society of Hematology, 99(10), 3771-3779.

Petersen, J. S., & Baird, S. K. (2021). Treatment of breast and colon cancer cell lines with anti-helmintic benzimidazoles mebendazole or albendazole results in selective apoptotic cell death. Journal of Cancer Research and Clinical Oncology, 147, 2945-2953.

Petroni, G., Bagni, G., Iorio, J., Duranti, C., Lottini, T., Stefanini, M., ... & Arcangeli, A. (2020). Clarithromycin inhibits autophagy in colorectal cancer by regulating the hERG1 potassium channel interaction with PI3K. Cell death & disease, 11(3), 161.

Pistritto, G., Trisciuoglio, D., Ceci, C., Garufi, A., & D'Orazi, G. (2016). Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging (albany NY), 8(4), 603.

Poynter, J. N., Gruber, S. B., Higgins, P. D., Almog, R., Bonner, J. D., Rennert, H. S., ... & Rennert, G. (2005). Statins and the risk of colorectal cancer. New England Journal of Medicine, 352(21), 2184-2192.

Qi, J. H., Wei, J. N., Zhang, Z. J., Dong, L., Zhang, L., Mao, Y. Y., ... & Bai, W. Q. (2021). A Meta-analysis on association between statins and colorectal cancer. Zhonghua liu Xing Bing xue za zhi= Zhonghua Liuxingbingxue Zazhi, 42(2), 343-350.

Qiao, X., Wang, X., Shang, Y., Li, Y., & Chen, S. Z. (2018). Azithromycin enhances anticancer activity of TRAIL by inhibiting autophagy and up-regulating the protein levels of DR4/5 in colon cancer cells in vitro and in vivo. Cancer Communications, 38, 1-13.

Raynal, N. J. M., Da Costa, E. M., Lee, J. T., Gharibyan, V., Ahmed, S., Zhang, H., ... & Issa, J. P. J. (2017). Repositioning FDA-approved drugs in combination with epigenetic drugs to reprogram colon cancer epigenome. Molecular cancer therapeutics, 16(2), 397-407.

Rebuzzi, S. E., Pesola, G., Martelli, V., & Sobrero, A. F. (2020). Adjuvant chemotherapy for stage II colon cancer. Cancers, 12(9), 2584.

Rissardo, J. P., Caprara, A. L. F., & Durante, Í. (2021). Valproate-associated movement disorder: a literature review. Prague Medical Report, 122(3), 140-180.

Rocha, G. Z., Dias, M. M., Ropelle, E. R., Osório-Costa, F., Rossato, F. A., Vercesi, A. E., ... & Carvalheira, J. B. (2011). Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. Clinical cancer research, 17(12), 3993-4005.

Saber, M. M., Galal, M. A., Ain-Shoka, A. A., & Shouman, S. A. (2016). Combination of metformin and 5-aminosalicylic acid cooperates to decrease proliferation and induce apoptosis in colorectal cancer cell lines. BMC cancer, 16, 1-12.

Sack, U., Walther, W., Scudiero, D., Selby, M., Kobelt, D., Lemm, M., ... & Stein, U. (2011). Novel effect of antihelminthic Niclosamide on S100A4-mediated metastatic progression in colon cancer. Journal of the National Cancer Institute, 103(13), 1018-1036.

Saito, T., Okada, S., Yamada, E., Shimoda, Y., Osaki, A., Tagaya, Y., ... & Yamada, M. (2015). Effect of dapagliflozin on colon cancer cell [Rapid Communication]. Endocrine Journal, 62(12), 1133-1137.

Sanford, S. L., Welfer, G. A., Freudenthal, B. D., & Opresko, P. L. (2020). Mechanisms of telomerase inhibition by oxidized and therapeutic dNTPs. Nature Communications, 11(1), 5288.

Schafranek, L., Leclercq, T. M., White, D. L., & Hughes, T. P. (2013). Clarithromycin enhances dasatinib-induced cell death in chronic myeloid leukemia cells, by inhibition of late stage autophagy. Leukemia & lymphoma, 54(1), 198-201.

Schjerning, A. M., McGettigan, P., & Gislason, G. (2020). Cardiovascular effects and safety of (non-aspirin) NSAIDs. Nature Reviews Cardiology, 17(9), 574-584.

Sehgal, S. N. (2003, May). Sirolimus: its discovery, biological properties, and mechanism of action. In Transplantation proceedings (Vol. 35, No. 3, pp. S7-S14). Elsevier.

Sekandarzad, M. W., van Zundert, A. A., Lirk, P. B., Doornebal, C. W., & Hollmann, M. W. (2017). Perioperative anesthesia care and tumor progression. Anesthesia & Analgesia, 124(5), 1697-1708.

Sheng, J., Sun, H., Yu, F. B., Li, B., Zhang, Y., & Zhu, Y. T. (2020). The role of cyclooxygenase-2 in colorectal cancer. International journal of medical sciences, 17(8), 1095.

Sherif, D. A., Makled, M. N., & Suddek, G. M. (2021). The HIV reverse transcriptase inhibitor Tenofovir suppressed DMH/HFD-induced colorectal cancer in Wistar rats. Fundamental & Clinical Pharmacology, 35(6), 940-954.

Shi, S., Zheng, H. C., & Zhang, Z. G. (2020). Roles of Fascin mRNA expression in colorectal cancer: Meta-analysis and bioinformatics analysis. Molecular and Clinical Oncology, 13(2), 119-128.

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer statistics, 2021. Ca Cancer J Clin, 71(1), 7-33.

Singleton, P. A., Moss, J., Karp, D. D., Atkins, J. T., & Janku, F. (2015). The mu opioid receptor: a new target for cancer therapy?. Cancer, 121(16), 2681-2688.

Slattery, M. L., Herrick, J. S., Lundgreen, A., Fitzpatrick, F. A., Curtin, K., & Wolff, R. K. (2010). Genetic variation in a metabolic signaling pathway and colon and rectal cancer risk: mTOR, PTEN, STK11, RPKAA1, PRKAG2, TSC1, TSC2, PI3K and Akt1. Carcinogenesis, 31(9), 1604-1611.

Sood, A. K., Armaiz-Pena, G. N., Halder, J., Nick, A. M., Stone, R. L., Hu, W., ... & Lutgendorf, S. K. (2010). Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. The Journal of clinical investigation, 120(5), 1515-1523.

Sood, A. K., Bhatty, R., Kamat, A. A., Landen, C. N., Han, L., Thaker, P. H., ... & Cole, S. W. (2006). Stress hormone–mediated invasion of ovarian cancer cells. Clinical Cancer Research, 12(2), 369-375.

Sorkin, E. M., Clissold, S. P., & Brogden, R. N. (1985). Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. Drugs, 30, 182-274.

Steinbach, G., Lynch, P. M., Phillips, R. K., Wallace, M. H., Hawk, E., Gordon, G. B., ... & Kelloff, G. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. New England Journal of Medicine, 342(26), 1946-1952.

Suehiro, Y., Takemoto, Y., Nishimoto, A., Ueno, K., Shirasawa, B., Tanaka, T., ... & Hamano, K. (2018). Dclk1 inhibition cancels 5-FU-induced cell-cycle arrest and decreases cell survival in colorectal cancer. Anticancer Research, 38(11), 6225-6230.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.

Talha B, Dhamoon AS. Ritonavir. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31335032

Tampakis, A., Tampaki, E. C., Nonni, A., Kostakis, I. D., Posabella, A., Kontzoglou, K., ... & Nikiteas, N. (2021). High fascin-1 expression in colorectal cancer identifies patients at high risk for early disease recurrence and associated mortality. BMC cancer, 21, 1-10.

Tanaka, H., Hino, H., Moriya, S., Kazama, H., Miyazaki, M., Takano, N., ... & Miyazawa, K. (2020). Comparison of autophagy inducibility in various tyrosine kinase inhibitors and their enhanced cytotoxicity via inhibition of autophagy in cancer cells in combined treatment with azithromycin. Biochemistry and biophysics reports, 22, 100750.

Thaker, P. H., Han, L. Y., Kamat, A. A., Arevalo, J. M., Takahashi, R., Lu, C., ... & Sood, A. K. (2006). Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nature medicine, 12(8), 939-944.

Thun, M. J., Jacobs, E. J., & Patrono, C. (2012). The role of aspirin in cancer prevention. Nature reviews Clinical oncology, 9(5), 259-267.

Toriyama, K., Takano, N., Kokuba, H., Kazama, H., Moriya, S., Hiramoto, M., ... & Miyazawa, K. (2021). Azithromycin enhances the cytotoxicity of DNA-damaging drugs via lysosomal membrane permeabilization in lung cancer cells. Cancer Science, 112(8), 3324-3337.

Toschi, E., Sgadari, C., Malavasi, L., Bacigalupo, I., Chiozzini, C., Carlei, D., ... & Ensoli, B. (2011). Human immunodeficiency virus protease inhibitors reduce the growth of human tumors via a proteasome-independent block of angiogenesis and matrix metalloproteinases. International journal of cancer, 128(1), 82-93.

Tsujii, M., & DuBois, R. N. (1995). Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. Cell, 83(3), 493-501.

Van der Jeught, K., Xu, H. C., Li, Y. J., Lu, X. B., & Ji, G. (2018). Drug resistance and new therapies in colorectal cancer. World journal of gastroenterology, 24(34), 3834.

Verma, S. K., Das, A. K., Gantait, S., Kumar, V., & Gurel, E. (2019). Applications of carbon nanomaterials in the plant system: a perspective view on the pros and cons. Science of the Total Environment, 667, 485-499.

Verma, S., Das, P., & Kumar, V. L. (2017). Chemoprevention by artesunate in a preclinical model of colorectal cancer involves down regulation of β-catenin, suppression of angiogenesis, cellular proliferation and induction of apoptosis. Chemico-biological interactions, 278, 84-91.

Vermunt, M. A., van der Heijden, L. T., Hendrikx, J. J., Schinkel, A. H., de Weger, V. A., van der Putten, E., ... & Beijnen, J. H. (2021). Pharmacokinetics of docetaxel and ritonavir after oral administration of ModraDoc006/r in patients with prostate cancer versus patients with other advanced solid tumours. Cancer Chemotherapy and Pharmacology, 87, 855-869.

Verschoor, Y. L., van den Berg, J., Beets, G., Sikorska, K., Aalbers, A., Van Lent, A., ... & Chalabi, M. (2022). Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

Vial, G., Detaille, D., & Guigas, B. (2019). Role of mitochondria in the mechanism (s) of action of metformin. Frontiers in endocrinology, 10, 442419.

Vidali, S., Aminzadeh, S., Lambert, B., Rutherford, T., Sperl, W., Kofler, B., & Feichtinger, R. G. (2015). Mitochondria: The ketogenic diet—A metabolism-based therapy. The international journal of biochemistry & cell biology, 63, 55-59.

Wang, Y., Liu, Y., Lu, J., Zhang, P., Wang, Y., Xu, Y., ... & Wei, G. (2013). Rapamycin inhibits FBXW7 loss-induced epithelial–mesenchymal transition and cancer stem cell-like characteristics in colorectal cancer cells. Biochemical and biophysical research communications, 434(2), 352-356.

Wassner, C., Bradley, N., & Lee, Y. (2020). A review and clinical understanding of tenofovir: tenofovir disoproxil fumarate versus tenofovir alafenamide. Journal of the International Association of Providers of AIDS Care (JIAPAC), 19, 2325958220919231.

Wild, C., Weiderpass, E., & Stewart, B. W. (Eds.). (2020). World cancer report: cancer research for cancer prevention. International Agency for Research on Cancer.

Williamson, T., Bai, R. Y., Staedtke, V., Huso, D., & Riggins, G. J. (2016). Mebendazole and a non-steroidal anti-inflammatory combine to reduce tumor initiation in a colon cancer preclinical model. Oncotarget, 7(42), 68571.

Wu, L., Lin, W., Liao, Q., Wang, H., Lin, C., Tang, L., ... & Zhao, L. (2020). Calcium channel blocker nifedipine suppresses colorectal cancer progression and immune escape by preventing NFAT2 nuclear translocation. Cell reports, 33(4).

Wu, Y., Xiab, R., Dai, C., Yan, S., Xie, T., Liu, B., ... & Huang, Q. Dexamethasone inhibits the proliferation of tumor cells. Cancer Manag Res [Internet]. 2019 Feb; 11: 1141–1154.[cited 2019 Apr 4].

Xie, L., Zhu, G., Shang, J., Chen, X., Zhang, C., Ji, X., ... & Wei, Y. (2021). An overview on the biological activity and anti-cancer mechanism of lovastatin. Cellular Signalling, 87, 110122.

Xu, L., Xia, H., Ni, D., Hu, Y., Liu, J., Qin, Y., ... & Xie, Y. (2020). High-dose dexamethasone manipulates the tumor microenvironment and internal metabolic pathways in anti-tumor progression. International Journal of Molecular Sciences, 21(5), 1846.

Xu, X. T., Hu, W. T., Zhou, J. Y., & Tu, Y. (2017). Celecoxib enhances the radiosensitivity of HCT116 cells in a COX-2 independent manner by up-regulating BCCIP. American journal of translational research, 9(3), 1088.

Xu, X., Wang, J., Han, K., Li, S., Xu, F., & Yang, Y. (2018). Antimalarial drug mefloquine inhibits nuclear factor kappa B signaling and induces apoptosis in colorectal cancer cells. Cancer science, 109(4), 1220-1229.

Xue, H., Li, J., Xie, H., & Wang, Y. (2018). Review of drug repositioning approaches and resources. International journal of biological sciences, 14(10), 1232.

Yang, J. L., & Friedlander, M. L. (2001). Effect of nifedipine in metastatic colon cancer with DNA mismatch repair gene defect. The Lancet, 357(9270), 1767-1768.

Yang, Y., Weng, W., Peng, J., Hong, L., Yang, L., Toiyama, Y., ... & Ma, Y. (2017). Fusobacterium nucleatum increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear factor– κB, and up-regulating expression of microRNA-21. Gastroenterology, 152(4), 851-866.

Yano, A., Fujii, Y., Iwai, A., Kageyama, Y., & Kihara, K. (2006). Glucocorticoids suppress tumor angiogenesis and in vivo growth of prostate cancer cells. Clinical Cancer Research, 12(10), 3003-3009.

Yatsunami, J., Turuta, N., Wakamatsu, K., Hara, N., & Hayashi, S. I. (1997). Clarithromycin is a potent inhibitor of tumor-induced angiogenesis. Research in experimental medicine, 197, 189-197.

Zeng, X., Liu, L., Zheng, M., Sun, H., Xiao, J., Lu, T., ... & Duan, Q. (2016). Pantoprazole, an FDA-approved proton-pump inhibitor, suppresses colorectal cancer growth by targeting T-cell-originated protein kinase. Oncotarget, 7(16), 22460.

Zhanel, G. G., Fontaine, S., Adam, H., Schurek, K., Mayer, M., Noreddin, A. M., ... & Hoban, D. J. (2006). A review of new fluoroquinolones: focus on their use in respiratory tract infections. Treatments in respiratory medicine, 5, 437-465.

Zhang, L., Liu, C., Jiang, Q., & Yin, Y. (2021). Butyrate in energy metabolism: there is still more to learn. Trends in Endocrinology & Metabolism, 32(3), 159-169.

Zhang, Z., Ji, J., & Liu, H. (2021). Drug repurposing in oncology: Current evidence and future direction. Current Medicinal Chemistry, 28(11), 2175-2194.

Zheng, W., Hu, J., Lv, Y., Bai, B., Shan, L., Chen, K., ... & Zhu, H. (2021). Pyrvinium pamoate inhibits cell proliferation through ROS-mediated AKT-dependent signaling pathway in colorectal cancer. Medical Oncology, 38, 1-9.