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REVIEW

Mechanism of 5-fluorouracil induced resistance and role of piperine and curcumin as chemo-sensitizers in colon cancer

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Abstract

Among cancer-related deaths worldwide, colorectal cancer ranks second, accounting for 1.2% of deaths in those under 50 years and 0.6% of deaths in those between 50 and 54 years. The anticancer drug 5-fluorouracil is widely used to treat colorectal cancer. Due to a better understanding of the drug's mechanism of action, its anticancer activity has been increased through a variety of therapeutic alternatives. Clinical use of 5-FU has been severely restricted due to drug resistance. The chemoresistance mechanism of 5-FU is challenging to overcome because of the existence of several drug efflux transporters, DNA repair enzymes, signaling cascades, classical cellular processes, cancer stem cells, metastasis, and angiogenesis. Curcumin, a potent phytocompound derived from Curcuma longa, functions as a nuclear factor (NF)-κB inhibitor and sensitizer to numerous chemotherapeutic drugs. Piperine, an alkaloid found in Piper longum, inhibits cancer cell growth, causing cell cycle arrest and apoptosis. This review explores the mechanism of 5-FU-induced chemoresistance in colon cancer cells and the role of curcumin and piperine in enhancing the sensitivity of 5-FU-based chemotherapy.

Clinical trial registration Not applicable

Keywords Colorectal cancer · 5- Fluorouracil · Chemoresistance · Piperine · Curcumin

Highlights

- 5-FU resistance occurs due to overexpression of the transporter protein and a change in its membrane dynamics due to ATP hydrolysis.
- 5-FU is effluxed from the cells due to overexpression of MRP5 (ABCC5) and MRP8 (ABCC11) transporters.
- Curcumin can reverse MDR by blocking NF-κB, upregulating cytochrome p450, and downregulating GST. It is a substrate of p-gp and has low bioavailability. Piperine can reverse MDR by competing with the ATP binding site, and it binds at NBD between the linker peptide and the consensus sequence of the Walker ATP loop.
- Piperine, when used as an adjuvant with curcumin, can increase its bioavailability by decreasing the rate of curcumin metabolic breakdown, increasing the residence time, changing the dynamics of membrane lipids, and altering the confirmation of enzymes in the intestine by blocking curcumin efflux through MDR transporters.

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Introduction

Colorectal cancer ranks second among the greatest number of deaths from other cancers, such as lung and prostate in men and lung and breast in women. CRC accounts for 48% of cases in men and 51% in women. The incidence, diagnosis, and patterns are customarily similar by sex but differ in terms of age. The incidences declined by a rate of 2% per year in people from 2014 to 2018, aged 50 years and above, and increased by 1.5% per year in people younger than 50 years (Siegel et al. 2022). Since the mid-1980s, there has been a decline in CRC incidences, but in the late 2000s, it accelerated in the United States and other developed countries (Siegel et al. 2017). The mortality rate decreased during the 2010–2019 decade by 2% per year but escalated among young adults. However, the death rate increased by 1.2% per year from 2005 to 2019 in people younger than 50 years and by 0.6% in individuals between 50 and 54 years (Siegel et al. 2022). The pre-determined incidence and estimated mortality rate of colorectal cancer in India is 36476 cases and 25690 cases, respectively. CRC is heterogeneous, and its pathogenesis is susceptible to various factors, including smoking, tobacco,

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consumption of alcohol, processed foods, and red meat, which contribute to the rapid progression and development of the disease (Sinha et al. 2015). Genetic susceptibility to colon cancer is mediated through polyposis and non-polyposis syndromes while mutations in DNA mismatch repair genes cause familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) (Baglioni and Genuardi 2004). 89% of tumors have at least one mutation in these pathways, while 59% of tumors have the diversification of being targetable by chemotherapeutic drugs. 39% of tumors require combinational therapies. Multidrug resistance, which the cancer cells develop in response to a variety of cancer treatments, is another factor contributing to the trial's failure. Most drugs have developed resistance against cancer cells, necessitating the need for a novel approach to overcome this resistance and ensure therapy efficacy. Intestinal microbiota and CRC are correlated, as the microbial community is responsible for maintaining homeostasis in the colon, including the biosynthesis of toxic compounds, chronic inflammation, and DNA impairment. The microbial community is further involved with chemotherapeutic drugs by interfering with drug efficacy and toxicity. Pectin is being used here as a transporter to deliver drugs to specific targeted areas of the colon. The colon's anaerobic bacteria generate the pectinase enzyme, which starts the process. One such drug is the antimetabolite drug 5-Fluorouracil, which is responsible for altering the intestinal microbiota (Das 2021). The drug showed variation in Lewis rats during the synthesis of microbiota from gram-positive to gram-negative bacteria after its administration. However, the population of anaerobic bacteria remains unchanged. 5-Fluorouracil is an antimetabolite drug that inhibits the normal functions of DNA and RNA in macromolecules, including essential biosynthetic processes.

Numerous studies have shown that curcumin, a naturally occurring flavonoid, has anti-cancer and MDR-inhibitory effects. Furthermore, flavonoids' antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory properties are well known. First-line therapy can be more effective when flavonoids are used as an antiproliferative medication. Curcumin and 5-FU together have the potential to improve the efficacy and potency of cancer therapies (Ferguson and Orlando 2015). Despite its vast array of benefits, curcumin has a low bioavailability. Therefore, curcumin's bioavailability rate can be increased by combining it with piperine, another flavonoid, which inhibits curcumin efflux through MDR transporters, increases residence time, changes the dynamics of membrane lipids, and changes the conformation of enzymes in the intestine (Hatab et al. 2019). Understanding the mechanism of 5-fluorouracil that causes cell death and by which cells undergo changes leading to efflux of the drug and upregulation of multidrug resistance proteins outcasts the properties of the resistance mechanism and is an essential step towards overcoming the resistance. This review illustrates the new combinatorial effect of curcumin and piperine acting as a chemosensitizer with 5-FU and addresses the problems associated with multi-drug resistance mechanisms leading to chemotherapeutic treatment failure in colon cancer.

Significance of 5-fluorouracil

5-FU, an analog of fluoropyrimidine, directly integrates into tumor cell DNA and RNA, inactivating thymidylate synthase and repairing DNA, but due to its low effectiveness, toxicity, and side effects, 5-FU has proven to be very limited (Azwar et al. 2021). Poor biopharmaceutical qualities of 5-FU, such as limited absorption, a short biological half-life (10–20 min), and fast catabolism, make the regimen difficult. Since 15–20% of patients developed drug resistance and 50–60% of patients had a recurrence risk, 5-FU treatment for colon cancer is challenging (Karthika et al. 2021). Since this drug overexpresses TS, nuclear transcription factors (NF-κB), cyclooxygenase-2 (COX-2), human epithelial growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF-1), and multidrug resistance gene 1, which encodes transporter P-glycoprotein (P-gp), MRP5, and MRP8 and exhibits dose-related toxic effects, its clinical use is limited (Karthika et al. 2021). NF-κB is a key factor in chemoresistance in conventional therapies and multidrug resistance, controlling genes related to cancer cell death and carcinogenesis, including COX-2, BCL-XL, BCL-2, P53, cyclin D1, and FAS. Prolonged exposure to 5-FU activates dysregulation of these genes (Li and Sethi 2010). An essential enzyme in the anabolism of 5-FU is thymidylate synthase (TS), which substitutes the hydrogen atom at the C5 position in 5-fluorouracil, an analog of uracil. This heterocyclic aromatic organic molecule is integrated into DNA and RNA in the same manner as pyrimidine and has a similar structure. mRNA levels increased in 5-FU-resistant cells, enhancing TS catalytic activity, decreasing TS transport, and/or inhibiting TS without altering its enzymatic activity. 5-fluorouracil's steady-state plasma concentrations range from 0.1 to 1.0 mM after bolus intravenous dosages of 400–600 mg/m2 (10–15 mg/kg). After intravenous treatment, 5-fluorouracil reaches CSF concentrations of around 7 μM in about 30 min due to its easy penetration across the blood-brain barrier. 5-fluorouracil plasma clearance ranges from 0.5 to 1.4 L/min for bolus doses. The binding of 5-fluorouracil to plasma proteins is 10%. Alpha-fluoro-beta-alanine, urea, carbon dioxide, and other inactive breakdown products are the principal by-products of

5-fluorouracil metabolism, which mostly takes place in the liver (Diasio and Harris 1989). Following 5-FU-based chemotherapy, ABCC5 (MRP-5) expression was significantly upregulated in CRC patients, which contributed to the growth of 5-FU resistance. A study by Oguri and his colleagues found that 5-FU induces ABCC11 (MRP-8) expression and that ABCC11 directly contributes to 5-FU resistance in human small-cell lung cancer cell lines via the efflux transport of the active metabolite FdUMP. According to another study, the high expression of ABCC11 in CRC tumors before chemotherapy may restrict the amount of ABCC11 that can be further induced by 5-FU treatment. A resistance factor for FPs (tyrosine-protein kinase / FEs) has been identified as ABCC11 deregulation (Oguri et al. 2007; Hlavata et al. 2012).

Mechanistic action of 5-FU

5-FU undergoes intracellular conversion to produce active metabolites like FUTP, FdUMP, and FdUTP, which disrupt thymidylate synthase's action. Dihydropyrimidine dehydrogenase (DPD) is an enzyme that regulates the rate of catabolism by catabolizing 5-FU to dihydro fluorouracil (DHFU), as shown in Fig. 1. The reduction of FOLATE 5,10-methylenetetrahydrofolate (CH2THF) to deoxythymidine monophosphate (dTMP) is catalyzed by TS as the primary methyl donor during the reductive methylation process of dUMP. The sole constant intake of thymidylate, which is necessary for DNA replication and repair, comes from this mechanism. The 36-kDa TS protein binds a nucleotide and CH2THF. It is a dimer consisting of two subunits. A stable TERNARY COMPLEX is formed by the 5-FU metabolite FdUMP with TS and CH2THF. This stops the typical substrate dUMP from binding and stops dTMP from forming. The key role of 5-FU activation is the conversion of FdUMP to FUP, which is then converted into FUTP and incorporated into RNA during transcription. It is phosphorylated to fluorouridine diphosphate (FUDP), which ribonucleotide reductase (RR) can then further phosphorylate to fluorouridine triphosphate (FUTP) or fluorodeoxyuridine diphosphate (FdUDP). Dihydropyrimidine dehydrogenase (DPD) is crucial for determining the efficacy and toxicity of 5-FU-based chemotherapy regimens. It breaks down in the liver up to 80% of 5-FU, forming α-fluoro-β-alanine (FBAL) and α-fluoro-β-ureidopropionic acid (FUPA), which are excreted through the kidneys, optimizing treatment, and minimizing patient adverse effects as shown in Fig. 1 (Aherne et al. 1996; Ghafouri-Fard et al. 2021). DNA damage is believed to result from imbalances in the dATP/dTTP ratio, which significantly hinder DNA synthesis and repair. TS inhibition causes dUMP

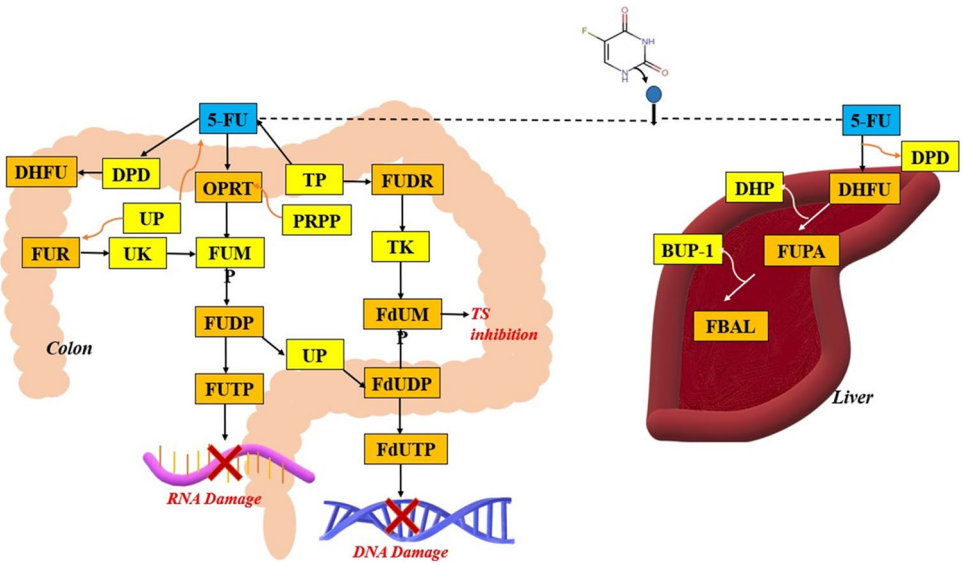

Fig. 1 5-Fluorouracil is a potent chemotherapeutic agent used in treating various cancers due to its ability to convert into three active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). These metabolites disrupt DNA synthesis and RNA processing, leading to cell death. DHFU – Dihydrofluorouracil, DPD—Dihydropyrimidine Dehydrogenase, OPRT – Orotate Phosphoribosyl transferase, TP—Thymidine Phosphorylase, FUDR – Floxuridine, TK—Thymidine Kinase, FDUM—5-Fluoro-2'-Deoxyuridine Monophosphate, FDUDP—5-Fluoro-2'-Deoxyuridine Diphosphate, UP—Uridine Phosphorylase, FUDP—5-Fluorouridine Diphosphate, FUTP—5-Fluorouridine Triphosphate, FUM—5-Fluorouridine Monophosphate, UK—Uridine Kinase, FUR—5-Fluorouracil Riboside, FUPA—5-Fluorouridine Phosphoribosyl transferase, FBAL—Fluoro-β-alanine, BUP-1—β-ureidopropionase-1, DHP—Dihydropyrimidine

aggregation, potentially increasing dUTP levels. High (F)dUTP/dTTP ratios prevent uracil-DNA-glycosylase from repairing uracil or 5-FU-containing DNA, leading to inaccurate nucleotide incorporation. Misincorporation of dUTP, a pyrophosphatase, leads to DNA strand breakage and cell death through repetitive cycles of excision, repair, and reinsertion. The pyrophosphatase dUTPase, which inhibits the intracellular accumulation of dUTP, significantly contributes to DNA damage resulting from dUTP misincorporation (Longley et al. 2003). The 5-FU metabolite FUTP disrupts RNA processing and functionality, leading to significant clonogenic potential loss in human colon cancer cell lines due to its significant incorporation into RNA. Pre-mRNA splicing is inhibited due to its impact on tRNA post-transcriptional modification, snRNA/protein complex assembly and activity, and tRNA post-transcriptional modification. 5-FU inhibits pseudouridine conversion in rRNA, tRNA, and snRNA species, preventing polyadenylation of mRNA at low doses (Zhang et al. 2008; Rai et al. 2023).

Immunogenicity of 5-FU

Myeloid-derived suppressor cells (MDSCs) can be specifically killed by 5-FU, thereby restoring anticancer immune responses (Mathew et al. 2023). Chemotherapy significantly affects the biology of regulatory T cells (Tregs) and MDSCs, two primary tumor-induced immunosuppressive cell types (Li et al. 2020). These cells are strong modulators of tumor immunity, which limits the effectiveness of cancer immunotherapy. MDSCs show high sensitivity to fluoropyrimidine due to inadequate expression of thymidylate synthase, the drug's target enzyme. Anticancer drugs like oxaliplatin and anthracyclines cause calreticulin expression in tumor cells, making them immunogenic (Gebremeskel and Johnston 2015). 5-FU, however, does not, indicating its primary mechanism of immunogenicity is MDSC removal. In vivo, 5-FU can specifically reduce MDSC. The enhanced therapeutic efficacy of 5-FU and CD8 + T-cell anticancer immune responses was partially recovered with the eradication of MDSCs. Current research has assessed another molecular pathway that is triggered by MDSCs' 5-FU-mediated cell death, which restricts its effectiveness and aids in immune evasion. 5-FU activates the NLRP3 inflammasome in MDSCs, causing IL-1 b production and IL-17 secretion. Blocking this cascade could improve 5-FU's anticancer efficacy. Improved efficacy in 5-FU-deficient mice is related to decreased tumor vasculature, supporting tumor growth through neo-angiogenesis (Ghiringhelli et al. 2007; Gabrilovich and Nagaraj 2009).

Toxicity of 5-FU

The second most common form of chemotherapy-induced cardiotoxicity is fluoropyrimidine cardiac toxicity, which can be exceedingly dangerous or even fatal. Myocardial infarction, ischemia, cardiomyopathy, dysrhythmia, sinoatrial, tako-tsubo cardiomyopathy, atrioventricular nodal dysfunction, cardiac arrest, QT prolongation with torsade de pointes, ventricular tachycardia, and sudden death are among the many symptoms that are linked to this condition. Alpha-fluoro-beta alanine has been related to both cardiotoxicity and neurotoxicity; other metabolites of 5-FU have also been linked to toxicity (Muneoka et al. 2005; Sorrentino et al. 2012). There is a strong correlation between 5-FU exposure and hematological and gastrointestinal damage. Furthermore, 5-FU has a somewhat limited therapeutic index. Two short prospective trials comparing patients with low DPD activity in PBM cells to those with normal DPD activity showed that 5-FU-related side effects were more common in these patients (Katona et al. 1998; Gamelin and Boisdron-Celle 1999). Myelosuppression, stomatitis, nausea, emesis, and diarrhea are among the adverse effects of 5-FU. Its toxicity is predictable in administration, scheduling, and dose. 15% of patients on a combinatorial 5-FU and leucovorin regimen had severe diarrhea. Although acute small intestinal toxicity is rare, individuals with severe ulceration and inflammation may experience vascular toxicity(Ansfield 1962; Fata et al. 1999).

Statistics of 5FU treatment, survival curve and resistance

Agents that act only after reaching the target are the focus of cancer pharmacology. Due to changes in the tissue environment, such as higher intratumoral pressure and lower levels of proteoglycan and hyaluronic acid, tumors may not respond to treatment. Neovascularization allows drugs to enter the tumor compartment, but the abnormal structure of new blood vessels can make drug delivery more challenging, as they may be leaky and disorganized (Mader et al. 1998). One major obstacle to long-term cancer treatment is acquired or innate resistance to anticancer medications. While intratumoral TS expression is associated with drug response or survival, overexpression of TS is proposed as the primary factor in 5-FU metabolism. The original tumor expression of p53 and TS are predictive markers for patients with advanced colorectal cancer (Paradiso et al. 2000; Fukushima et al. 2001). In advanced colorectal cancer, 5-FU plus other chemotherapeutic drugs have increased response rates from 40 to 50%. After two years, only 12% of patients are still alive. The efficacy of 5-FU-based chemotherapy is hampered by both acquired and de novo chemoresistance. All non-responding tumors are not caused by high TS expression,

and 5-FU sensitivity is impacted by expression levels, p53 genetic status, and DNA mismatch-repair genes (Wang et al. 2004). Patients with stage I and stage II cancer had survival rates of 91% and 82%, respectively, but patients with metastatic illness had survival rates of only 12%. Individuals with stages I and II have a 30% risk of recurrence following surgery, whereas individuals with stages III have a 50–60% chance. This difference highlights the need for early detection and treatment (Miller et al. 2019; Huang et al. 2022). Approximately 50% of patients with colorectal cancer (CRC) will eventually die due to the spread of the cancer to other parts of the body. Chemotherapy, compared to just receiving supportive care, increases the average lifespan of patients with metastatic CRC. Therefore, palliative chemotherapy is offered to these patients to alleviate symptoms, maintain their quality of life, and improve survival. Clinical trials, even when using similar criteria to select patients, often show a wide range of survival rates. This is usually attributed to differences in patient characteristics or factors that affect prognosis. Patients participating in randomized trials are typically grouped based on their performance status, but other prognostic factors or their combination may have a greater impact on patient survival than any promising cancer-fighting drug or treatment combination. Several clinical parameters, including performance status, white blood cell (WBC) count, elevated lactate dehydrogenase, elevated liver transaminases, serum albumin, level of hemoglobin or platelets, pathological grading, localization of the primary tumor, or tumor markers like carcinoembryonic antigen (CEA), have been identified as prognostic markers in a limited number of studies involving fewer than 400 patients. There is a lack of agreement and widespread approval on the significance of certain prognostic variables (Köhne et al. 2002). Due to the drug's brief half-life, various schedules of extended 5-FU continuous infusion have been tested to prolong the duration of tumor cell exposure. In addition, treatment of 5-FU permitted a 5-FU dose intensity of 5000 mg/m2/week and 8400 mg/m2/week using monthly 5-day continuous infusion and 28-day continuous infusion, respectively, compared to 2000 mg/m2/week using monthly 5-day IV bolus. Three randomized trials demonstrated that both 5-day and protracted multiweek infusions resulted in higher response rates compared to traditional bolus regimens. Nevertheless, they did not enhance survival. The enhanced rates of response were achieved while also experiencing dramatically reduced rates of severe hematological and gastrointestinal damage. In addition, the extended administration of the medication resulted in hand-foot syndrome, which required dose reductions for approximately 25% of the patients. Retrospective investigations have convincingly indicated a correlation between the dose of 5-FU and the response to 5-FU in metastatic colorectal cancer. However, the use and advancement of high-dose methods have been impeded by the hematological and mucosal toxicity that limits the dosage. Shah discovered a significant benefit in administering a 48-h 5-FU infusion every week when evaluating three different schedules of 5-FU. The response rates were enhanced in three randomized studies by utilizing continuous infusion schedules of 5-FU. This improvement may be attributed to the ability to intensify the dosage with a distinct toxicity pattern, typically less severe than that of intravenous bolus administration. An 8-h uninterrupted infusion seemed to be a favorable solution that balanced two limitations: the need for a continuous infusion to achieve a stable concentration level, and the desire to avoid a full day of hospitalization (Gamelin and Boisdron-Celle 1999). 5-FU exhibits a limited therapeutic dosage range and its administration shows substantial interindividual variability, sometimes leading to increased toxicity. The significant variations in individual responses to 5-FU treatment indicate that relying just on body surface area to determine the dosage of 5-FU is inadequate. Furthermore, clinical studies have not demonstrated a substantial association between the dosage of 5-FU determined by body surface area and clinical response. However, the pharmacological characteristics of 5-FU in vivo did exhibit a significant correlation. Several investigations have shown a strong association between the region below the plasma concentration-time curve (AUC) and the toxicity of 5-FU. Within a living organism, 5-FU hinders the activity of thymidylate synthetase (TS), which prevents the production of DNA. Additionally, it undergoes metabolism via dihydropyrimidine dehydrogenase (DPD) to produce metabolites that are no longer active. The levels of TS and DPD vary among individuals, with DPD levels exhibiting a typical population-wide variation of up to 20-fold (Etienne et al. 1995; Fang et al. 2016). According to recent studies, the administration of the FOLFOX treatment in patients with colorectal cancer resulted in a significant variation in the concentration of 5-FU, with the maximum and lowest levels differing by up to 100-fold among different individuals (Dong et al. 2005).DPD and TS have significant functions in the process of 5-FU biotransformation. It was expected that the level of DPD expression would have a negative correlation with AUC since DPD breaks down 5-FU. The expression of TS could serve as an indicator of sensitivity to 5-FU. The prevalence of DPD in this group of patients is 38.96%, significantly less than the 73.58% reported by Xiao et al. (Xiao et al. 2005). Fang and his colleagues conducted a study on the first phase of colorectal cancer (CRC) and proposed that the administration of 5-FU therapeutic dosage exhibited significant variation across different areas. For instance, Chinese colorectal patients were shown to have an ideal therapeutic dosage ranging from 28.03–38.94 mg·h/L. Administering an ideal therapeutic dose has the potential to increase the effectiveness of treatment and enhance the overall quality of life for patients. The expression of DPD and

TS could potentially function as biomarkers in the development of treatment plans, however, their specific roles require additional investigation (Fang et al. 2016).

Patients diagnosed with recurrence or advanced colorectal cancer typically experience a bleak prognosis, with a median survival of less than two years. Administration of 5-fluorouracil (5-FU) either alone or in conjunction with CPT11/irinotecan or oxaliplatin leads to a modest improvement in survival rates. However, most patients ultimately succumb to the disease. Colorectal cancer of different stages has been characterized by a significant number of genetic alterations. Several of these are linked to natural history and the act of surviving. Microsatellite instability (MSI) is linked to a more positive prognosis, while chromosome 18q deletions are linked to reduced survival in stage II and III colorectal cancer. Currently, there are no identified genetic indicators that can predict survival in patients with advanced colorectal cancer. In this type of cancer, the occurrence of microsatellite instability (MSI) is uncommon, while the deletion of chromosome 18 is more prevalent (Shen et al. 2007). Patients with stage II or III illness, whose tumors exhibit proficient mismatch repair status, experienced significant advantages from 5-FU chemotherapy. Enhancing their total survival and disease-free survival by nearly 20%. Nevertheless, individuals with MMR-deficient tumors do not appear to have any advantages from 5-FU adjuvant chemotherapy(Jover et al. 2009). Jiang and his colleagues have shown that the methylation of WNT5A is linked to a more favorable response to treatment in colorectal cancer (CRC) patients who were treated with 5-FU as their initial therapy. Furthermore, the expression of the WNT5A gene can be reinstated by removing the methylation in hypermethylated colorectal cancer (CRC) cells. The amount of WNT5A expression is inversely related to the tumor suppression caused by 5-FU, and it can be studied further as a biomarker to determine its prognostic significance and to guide treatment selection in CRC (Jiang et al. 2017).

Chemoresistance mechanisms and drug transporters

The elevated expression of ABC transporters in many malignancies and in some drug-resistant cell lines is a major factor in the development of multidrug resistance (MDR) (Amawi et al. 2019). There are 48 members of the ABC transporters superfamily, all of which have similar structural and functional characteristics (Wilkens 2015). Tumor cells' increased efflux capacity, mediated by membrane transporters in the ABC superfamily, lowers drug accumulation and is a key mechanism of MDR. The ATP-binding cassette (ABC) superfamily, divided into seven groups A to G, is responsible for active drug efflux. Of these ABC families, the increased expression of ABCC1 (MRP1), ABCG2 (MXR), and ABCB1 (P-gp) is linked to the classical MDR (Marquez and Van Bambeke 2011). Drug resistance Transporters are essential for their significance in:

- Absorption, distribution, metabolism, excretion, and toxicity of drugs
- morphogenesis and stem cell development.
- to gain an understanding of the biology underneath every transport system
- change membrane transport through either increased or decreased drug absorption.
- disrupt or change the target enzyme expression.
- alter how those drugs are activated or degraded.
- improved DNA repair and suppressed apoptosis.
- altered membrane transport in tumor cells, also known as the classical MDR mechanism (Glavinas et al. 2004).

The additional resistance mechanisms include the upregulation of survival pathways and insensitivity to drug-induced apoptosis because death pathways are blocked. When cancer cells are given chemotherapy, the ratio of pro-to-anti-apoptotic members or death-to-survival signals establishes the threshold for apoptosis. Drug sensitivity and resistance are strongly correlated with deregulation in one or both pathways. Certain cancer forms exhibit innate resistance to chemotherapy because of genetic and epigenetic modifications, making them resistant to treatment even after initial chemotherapy exposure. According to the Goldie-Coldman theory, one in every million cancer cells has an innate resistance to a certain class of medications or chemotherapeutic agents. This theory is based on understanding the rates of intrinsic mutations in mammalian cells as well as the kinetics of the cancer cell population. Every cell experiences frequent damage to its DNA, and although DNA repair is not flawless, base misincorporation happens at a consistent rate of 10^6 bases, despite DNA polymerase being an efficient enzyme (Diaconu et al. 1999; Liu 2009). Chemotherapy eliminates drug-sensitive cells, leaving a greater percentage of drug-resistant cells (Hochhauser and Harris 1991).

Drug influx and efflux mechanism

From prokaryotes to humans, all species belong to the superfamily of ATP-binding cassette transporters. Transporters attach to ATP and release different substrates across the cell membrane to prevent the buildup of toxins and medications. This protects the cells against xenobiotics. They are made up of two less conserved transmembrane domains and two highly conserved cytoplasmic domains. P-gp can hydrolyze ATP molecules and pump drug molecules or toxic substances from within cells to the outside. It is

present in various cells, including the intestinal epithelium, liver, colon, kidney, and blood-brain barrier. MDR1 or p-gp is GSH-dependent and can only transmit modified drugs, affecting their metabolic activity. As a result, it affects when the drugs become metabolically active. In general, it has been found that overexpression of these transporters within tumor cells decreases the buildup of lethal doses of drugs in the cells, promoting the progression of cancer cells and the emergence of multidrug resistance (Zhou et al. 2008). Drug breakdown, alteration, or drug binding to other molecules are examples of changes affecting drug activation. However, following the initiation of treatment, the drug's toxic effect is typically diminished and the cancer cells' ability to activate the drug is compromised. Uridine diphosphate glucuronosyltransferase (UGT), glutathione S-transferase (GST)/glutathione S-hydrolases (GSH), and cytochrome P-450 (CYPs) are crucial enzymes for drug activation and inactivation (Danielson 2002; Keyvani-Ghamsari et al. 2020). Drugs become inactive due to mutations in the cytochrome p450 genes. Increasing the GST-GSH system's activity helps drugs become inactive and shield cells from chemotherapy. Furthermore, its attachment to GSH makes it more soluble and improves the likelihood that MDR proteins will be able to remove the drug from the cell (Talalay 2000). Apart from the increased drug efflux resulting from distinct drug transporters linked to tumor cells, cancer cells may also utilize drug redistribution to decrease intracellular drug load. Lung resistance-related protein (LRP), a 110-kD non-ABC drug transporter vault protein, is responsible for this drug's redistribution. In patients with acute myelogenous leukemia, ovarian cancer, and other malignancies, elevated vaults in MDR cancer cell lines indicate resistance to drugs and a dismal prognosis (Scheffer et al. 1995; Dalton and Scheper 1999). Drugs just do not enter cells; instead, regular dietary intake transport is carried out by around 400 distinct solute carriers. Studies have shown that about 10% of other substances that operate on cells influence the absorption of certain drugs, and changes in the quantity or selectivity of these transporters can lead to drug-resistant cells (Hembruff et al. 2008).

MRP/ABC transporter

MRP is a drug-resistant gene, as demonstrated by earlier studies, however, its exact mode of action is unknown. MRP was not found in the same subcellular location as P-gp, a transporter-like protein found in the plasma membrane. MRP (190 KDa) was found in an endoplasmic reticulum (ER) apart from the plasma membrane. In most cases, the actions of MRP differ from those of the drug transporter P-gp. Like P-gp, MRP may show resistance to a variety of hydrophobic medications. Drug accumulation in cells can be inhibited by MRP, and this mechanism can be stopped by permeabilizing the plasma membrane. MRP can enhance drug efflux from cells (Sharom et al. 2001; Daleke 2003; Sanchez-Covarrubias et al. 2014). ABC transporters are classified as ATP-dependent trans bilayer lipid transporters into two categories: exofacially directed floppies and cyto facially directed flippases. ABC transporters, which are a type of flippase, function as hydrophobic vacuum cleaners, eliminating non-polar compounds from the membrane bilayer (Hyde et al. 1990). Proteins are categorized according to the Walker A and B motifs found in their nucleotide-binding domains (NBDs), which are made up of 90–120 amino acids (Kerr 2002). Two TM domains with six to eleven membrane-spanning helices make up an ABC transporter, or two NBDs and two TM domains make up a functioning transporter. Because 5-FU has a complicated metabolism, it has been claimed that ABCC5 and ABCC11, which are the active transporters for FdUMP, confer resistance to 5-FU and several fluoropyrimidines (Guo et al. 2003; Öman et al. 2021).

MRP5/ABCC5

MRP5 is a homolog of MRP1 and initially emerged through database screening of translated sequencing tags. It was anticipated that MRP5 would be a brief MRP without the extra MSD0. MRP5 transports cyclic guanosine monophosphate (cGMP), cAMP, and PMEA (an antiretroviral molecule). Consequently, MRP5 might have a role in the control of physiological processes and has a low affinity for substrates based on nucleotides. In addition, MRP5 acts as an exporter of folate. MRP5 expression has been found widely in human tissues, including carcinomas including the liver, placenta, and cornea (Zhang et al. 2015a, b). MRP5 plays a role in inducing resistance to various anticancer drugs such as MTX, 5-FU, and cisplatin, as revealed in in vitro studies (Pratt et al. 2005; Elfadadny et al. 2021). The ABCC5 substrates that are frequently used for flow cytometry assays are BCECF, Fluorochrome, Fluorescein, and 5-chloromethyl fluorescein diacetate (CMFDA) (Guo et al. 2003). 5-Chloromethylfluorescein diacetate, or CMFDA, is a membrane-permeable, non-fluorescent compound that is intracellularly broken down by esterase into a membrane-impermeable, fluorescent, negatively charged, thiol-reactive intermediate called CMF which is trapped inside the cell due to its polar nature. Due to overexpression of MRP5, fluorescent CMFDA is released from a resistant cell upon ATP hydrolysis (Pratt et al. 2006). Dinitrophenyl glutathione, GSH, and acidic organic dyes can all be pumped out by the MRP5 (Reid et al. 2003; Bai et al. 2004). Current Research indicates that platinum-containing drugs like cisplatin, oxaliplatin, 5-FU, methotrexate, pemetrexed, and doxorubicin exhibit cross-resistance due to MRP5. MRP5 is unique from other MRPs since it does not have an N-terminal MSD.

The localization of MRP5 to basolateral membranes was reported. As a result, MRP5 travels to the basolateral membrane where it transports specific classes of drugs as well as organic anions (Wijnholds et al. 2000; Glavinas et al. 2004).

MRP8/ABCC11

MRP8 is an amphipathic anion transporter, discovered in 2003, and is capable of effluxing pyrimidine and purine nucleotide analogs, such as cAMP and cGMP. It was anticipated that MRP8 would be a brief MRP with 12 TM helices. Two potential binding sites within the MRP8 homology model were proposed in the absence of the crystal structure. MRP8 shares similarities with MRP4 and MRP5 due to the absence of a third membrane-spanning domain, while sequence comparisons with other MRP family members reveal a close resemblance to MRP5 (Guo et al. 2003; Kruh and Belinsky 2003). MRP8 is found in human PNS and CNS axons and may be involved in physiological processes. MRP8 may be implicated in physiological processes involving glucuronides, steroid sulfates, and bile acids, according to research on membrane vesicles (Dallas et al. 2006; Zhang et al. 2015a, b). MRP8 is physiologically linked to axillary odor and cerumen (earwax) secretion (Toyoda and Ishikawa 2010). MRP8 is responsible for the effluxion of various therapeutically significant nucleoside analogs, including 5-fluorouracil, 5-fluoro-5'-deoxyuridine (PMEA), and 5-fluoro-2'-deoxyuridine. There is a splicing variant of ABCC11 where exon 28 is removed, although its purpose is still unknown (Yabuuchi et al. 2001).

Cancer stemness

According to the concept of cancer stem cells (CSCs), cancers contain distinct undifferentiated cells that have traits of stem cells, such as self-renewal ability, heterogeneity, and resistance to radiation and chemotherapy. CSCs exhibit resistance to chemotherapy due to slow proliferation and resistance mechanisms, such as ABCC transporters. They may be spared in treatments causing tumor shrinkage, allowing regrowth (Atashzar et al. 2020). According to recent research, cancer stem cells in the tumor microenvironment are principally responsible for the enhanced stemness that results in 5-FU resistance in cancer cells (Pan et al. 2021). Traditional chemotherapy targets fully developed cancer cells, which permits weakly differentiated and dormant CSCs to relapse. The establishment of quiescent states, metabolic switches, aberrant growth signaling pathways, and DNA damage resistance have all been connected to 5-FU resistance in CSCs. Important properties of CSCs include multidrug resistance and the efflux of PI or Hoechst 33,342 via ATP-binding cassette transporters(McIntosh et al. 2016). Cancer stem cells lose homeostasis, leading to constitutive Wnt signal activation due to gene mutations. This leads to adult stem cell cancer in hair follicles, breasts, and skin crypts. Sporadic colorectal cancer is primarily caused by a loss of APC function or oncogenic β-catenin mutations. Variable intracellular distribution of the Wnt signaling protein is also observed as shown in Table 1 (Schatoff et al. 2017). Nuclear β-catenin staining was specifically observed in tumor cells moving to nearby stromal tissues. As a result, varying degrees of Wnt signaling activity represent the heterogeneity of tumors. They could account for several cellular processes that, in turn, stimulate tumor growth and malignant behavior, such as proliferation and the epithelial-mesenchymal transition (Brabletz et al. 2005; Fodde and Brabletz 2007). Wnt3a binds to the Wnt/β-catenin pathway and activates p38 MAPK. A β-catenin chromatin-related kinase called p38α regulates the signaling pathway that is connected to colorectal cancer tumor development, metastasis, and chemoresistance. (Zhao et al. 2022). ASCL2, a key protein in the Wnt signaling pathway, is a key marker in colorectal cancer stem cells, preserving their characteristics and contributing significantly to their development as shown in Table 1 (Wang et al. 2021a). Growth signaling pathway activation, quiescent state, microRNA dysregulation, metabolic switch, and phenotypic plasticity are all associated with CSCs in colorectal cancer and are linked to therapeutic resistance. Wnt/catenin signaling activity targets Lgr5 (Table 1) and other putative markers (Alvarado-Ortiz et al. 2019).Notch activation is crucial for maintaining CSC phenotypic traits, and blocking Notch signaling with DAPT in vitro inhibited cell proliferation and reduced chemoresistant and ionosphere cell numbers (Das et al. 2020). PI3K/AKT is linked to 5-FU resistance and CSC-like characteristics in metastatic-associated colon cancer 1 (MACC), with MACC1 elevated in 5-FU-resistant cells (Table 1), and MACC1 knockdown decreasing MDR1 expression (Wang et al. 2017).

Epigenetic alterations

The epigenome undergoes modifications during carcinogenesis, including global changes in histone modification marks, DNA methylation loss, localized hypermethylation, and changes in miRNA production (Zhao and Shilatifard 2019). The MDR phenotype in cancer cells is acquired when the ABCB1 gene is demethylated, reducing anticancer drug accumulation. Epigenetic changes can impact DNA repair machinery, like in colorectal cancer. Combining standard chemotherapeutics with epigenetic medications like DAC can successfully treat resistant tumors. Although DAC doesn't directly stop tumor growth, it prevents DNA methylation, making the tumor more susceptible to 5-FU (Verbrugge et al. 2011). Epigenetic changes such as chromatin remodeling, DNA methylation, histone modifications, and

Table 1 Markers of cancer stem cells, genes of epigenetic regulation, signaling pathways, and growth factors involved in colon cancer cells

Genes/ Markers/Transcription factors/Proteins	Functions	References
CD29	Act as a cell adhesion molecule	(Hatano et al. 2017)
LGR5	Protein member of the Wnt family	(Hirsch and Ried 2016)
MSI-1	RNA-binding protein	(Femia et al. 2013)
DCAMKL-1	Intracellular protein/kinase	(Femia et al. 2013)
ASCL 2	A transcription factor involved in WNT signaling	(Shang et al. 2015)
CD133	Promotes angiogenesis and metastasis	(Glumac and LeBeau 2018)
CD44	Involved in metastasis/ a receptor of hyaluronic acid	(Jing et al. 2015)
CD166	Cell adhesion molecule of ECM	(Shafaei et al. 2013)
CD24	Heat-stable antigen/ cell adhesion molecule	(Nosrati et al. 2016)
ESA	Cell-to-cell signaling and adhesion molecule	(Tseng et al. 2015)
ALDH1	Promotes metastasis and regulates cell proliferation	(Holah 2017)
SOX2	Angiogenesis, vascularization, and metastasis	(Lundberg et al. 2016)
EPCAM	Formation of Wnt-mediated cancer stem cells (CSCs) and their resistance to therapy in CRC	(Munz et al. 2009)
APC	Extensive differentiation of tumor cells, maintenance of inhibition of carcinoma without any relapse	(Dow et al. 2015)
β-CATENIN	Promotes transcription of targeted genes and therapy resistance in CRC	(Dow et al. 2015)
WNTs	Excessive activation of the Wnt/β-catenin signaling pathway promotes the maintenance of stem cell properties	(Dow et al. 2015)
NOTCH-1	Enhances the phenotypic of cancer stem cells (CSCs) and promotes the proliferation of therapy-resistant colon cancer cells	(Huang et al. 2015)
HES-1	Shields cancer stem cells from undergoing differentiation	(Huang et al. 2015)
GLI-1	Promotes Hedgehog signaling and therapy resistance in CRC	(Usui et al. 2018)
YAPI	Enhances resistance to therapy in colon cancer and a lower survival rate among patients	(Wierzbicki and Rybarczyk 2015)
YESI	Regulates YAP1 expression by YES1 and plays a role in the treatment resistance of colon cancer	(Touil et al. 2014)
MACCI	Enhances the production of spherical structures and upregulates the expression levels of pluripotent markers: CD44, CD133, and Nanog	(Wang et al. 2017)
ABC TRANSPORTERS	Initiates histone deacetylation and chemosensitivity, silences ABC transporters	(Sparreboom et al. 2003)
ASC	Initiates DNA methylation and chemoresistance	(Ohtsuka et al. 2006)
BNIP3, DAPK	Initiates DNA methylation and chemoresistance, reduces apoptosis	(Sugita 2011)
DPYD	Promotes DNA methylation and histone deacetylation and induces capecitabine/5-FU chemosensitivity	(Noguchi et al. 2004; Sato et al. 2006)
MGMT	Induces DNA methylation and silences MGMT	(Dunn et al. 2009)
SPARC	Induces DNA methylation and silences SPARC; Chemoresistance	(Cheetham et al. 2008)
TYMP	Promotes DNA methylation, TYMP silencing, TYMS upregulation and histone acetylation	(Kosuri et al. 2010)
UGTIAI	Promotes DNA methylation and silences UGTIAI	(Bélanger et al. 2010)
UMPK	Initiates DNA methylation and capecitabine/5-FU chemoresistance	(Humeniuk et al. 2009)
TGF-β	Upregulated in CRC cells, involved in 5-FU resistance and its inhibition restores the sensitivity of CRC cells resistant to 5-FU	(Romano et al. 2016)
FGFR4	Initiates EMT, promotes tumor-stroma interaction and 5-FU resistance	(Liu et al. 2013a)
Soluble Growth factor	Initiate carcinogenesis and involved in TME-associated resistance; stimulates JAK/STAT, PI3K/AKT signaling pathways	(Martelli et al. 2012)
EGFR	Promotes 5-FU resistance	(Shen et al. 2018)

Abbreviations: *CD29*, Cluster of Differentiation 29; *LGR5*, Leucine-rich repeat-containing G-protein coupled receptor 5; *MSI-1*, Musashi-1; *DCAMKL-1*, Doublecortin and CaM Kinase-Like-1; *ASCL 2*, Achaete-Scute Family BHLH Transcription Factor 2; *CD133*, Cluster of Differentiation 133; *CD44*, Cluster of Differentiation 44; *CD166*, Cluster of Differentiation 166; *CD24*, Cluster of Differentiation 24; *ESA*, Epithelial Specific Antigen; *ALDH1*, Aldehyde Dehydrogenase 1; *SOX2*, SRY-Box Transcription Factor 2; *EPCAM*, Epithelial Cell Adhesion Molecule; *APC*, Adenomatous Polyposis Coli; *β-CATENIN*, Beta-Catenin; *WNTs*, Wingless/Integrated; *NOTCH-1*, Neurogenic Locus Notch Homolog Protein 1; *HES-1*, Hairy and Enhancer of Split-1; *GLI-1*, GLI Family Zinc Finger 1; *YAPI*, Yet Another PI; *YESI*, Yeast Enhancer of Split Homolog 1; *MACCI*, Malate Aspartate Shuttle Complex Citrate Carrier; *ABC TRANSPORTERS*, ATP-Binding Cassette Transporters; *ASC*, Apoptosis-associated Speck-like protein containing a CARD; *BNIP3*, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; *DAPK*, Death-associated protein kinase; *DPYD*, Dihydropyrimidine Dehydrogenase; *MGMT*, O-6-Methylguanine-DNA Methyltransferase; *SPARC*, Secreted Protein Acidic and Rich in Cysteine; *TYMP*, Thymidine Phosphorylase; *UGT1A1*, UDP Glucuronosyltransferase Family 1 Member A1; *UMPK*, Uridine Monophosphate Kinase; *TGF-β*, Transforming Growth Factor Beta; *FGFR4*, Fibroblast Growth Factor Receptor 4; *Soluble Growth factor*,

Table 1 (continued)

Generic term for growth factors that are secreted and function in a paracrine or autocrine manner; *EGFR*, Epidermal Growth Factor Receptor

noncoding RNAs are frequently linked to the development of colorectal cancer (Mohammad et al. 2019). Direct hypermethylation of a single allele, DNA hypomethylation, or the promoter CpG island methylation in tumor-suppressors Krüeppel-like factor 6, KLF4, and ZNF726—as observed in CDKN2A, LINC00460, and ZNF726 silencing—can all lead to genomic instability and the start of tumors in colon cancer (Dong et al. 2022). Research suggests that 5-FU resistance in colon cancer patients may be due to methylation mechanisms, specifically silencing PCDH17 through promoter methylation, which inhibits its tumor-suppressor function and causes JNK-dependent autophagic cell death (Liu et al. 2019). According to a study, 5-FU resistance can be brought on by promoter hypermethylation, which involves the EGFR (Table 1) and p53 signaling pathways, cytochrome P450-mediated drug metabolism, and pyrimidine metabolism. Histone deacetylases, promoter hypermethylation of miR-181a/135a/302c (Table 2), tolerance, and microsatellite instability/stable state are all associated with 5-FU resistance in colon cancer cells (Shi et al. 2018).

Growth factors

MDR cancer cells produce more growth factors autocrineally than drug-sensitive tumor cells, including interleukin (IL)-1, IL-4, IL-6, and IL-8. These factors affect metabolic rate, differentiation, proliferation, and death. Solid and metastatic tumors can contain higher concentrations of exogenous fibroblast growth factors, improving cancer chemoresistance. Drugs like 5-FU are impotent against high concentrations of these factors. Suramin, an inhibitor of these factors, reversed a tenfold increase in resistance when combined with intracellular and extracellular factors (Bukowski et al. 2020). Multiple pathways are activated by the epidermal growth factor receptor (EGFR), such as PI3K/Akt/mTOR, src/FAK/ROS, and JAK/stat3 (Table 1). Overexpression can activate STAT3 and NF-κB, leading to poor prognosis and chemoresistance. MiR-20b inhibits ADAM9/EGFR pathway in colon cancer cells (Kalita et al. 2023). For growth factor receptors to become active, they do not require any ligand at all or even just their typical ligand. Cell membrane receptors that are generated by the same cell are stimulated autocrinally by a ligand generated by that cell. Intracellular constituents of the receptor molecule or additional signal transduction mediators are stimulated by intracrine stimulation, which is another potent effector of growth factor action, even on dysfunctional receptors (Sporn and Todaro 1980; Ricort and Binoux 2002).

miRNAs

Small nucleolar RNAs (snRNAs), long non-coding RNAs (lncRNAs), piwi-acting RNAs (piRNAs), microRNAs (miRNAs), and circRNAs are the several forms of non-coding RNAs (ncRNAs), which are oncogenic drivers and implicated in tumor growth and distributed across many cancer types and are incapable of coding proteins. Growing data suggests that dysregulation of non-coding RNAs (ncRNAs) may be a possible therapeutic target for reversing cancer chemoresistance, as it can decrease the uptake of anti-tumor drugs or boost the expression of ABC transporters through a variety of pathways (Anastasiadou et al. 2018; Zhang et al. 2020b). In colorectal cancer, it has been discovered that miR-21, miR-224, miR-215, miR-222, miR-320, miR-140, miR-143, and miR-34a have important therapeutic and/or chemo-sensitizing effects. (Mazeh et al. 2013). Research has indicated that miRNAs can control the expression of ABCC transporters by attaching to their 3′UTR. Moreover, microRNA may be the cause of dysregulated transcription and translation efficiency, steric blockage on the mRNA target, or translational reprogramming. Upon administering 5-FU, CRC cells (Table 2) exhibited both downregulated and elevated miRNA expressions in comparison to healthy cells. These changes in miRNA expression after chemotherapy imply that miRNAs are involved in regulating 5-FU responses in colorectal cancer cells. Certain miRNAs act as tumor suppressors—tumors that are downregulated and encourage 5-FU resistance—while others act as oncogenes, or those that are upregulated and cause 5-FU resistance.

Microenvironmental factors, EMT, and Warburg's effect

Although not all metastatic cancers show EMT, the concept is controversial in oncology because EMT's contribution to the invasion of metastasis cascade is confused by the mutation load of primary tumor cells, particularly for the final stage of host tissue colonization (Ye and Weinberg 2015). Researchers speculate that partial EMT facilitates the return to an epithelial phenotype necessary for the metastatic locations to resume proliferation (Hong et al. 2018). TME features induce the phenotypic changes necessary to increase cell motility and start the invasion, but they are essentially unable to sustain it until the cells have left the original site. This makes it easier for the reverse transition to occur when the cells are faced with a new physiologically distant environment. This process enhances migration potential and alters the cytoskeleton, the two functional hallmarks of EMT (Thiery 2002). The lack of cell-to-cell adhesion

Table 2 Effect of miRNA on 5-FU and colorectal cancer indicating the upregulation and downregulation of miRNA expression and the targets and factors associated with it

MicroRNAs	Functions	Targets/Factors	Expression	References
miR-449b	Inhibition Of CSCs	CYCLIN D1 AND E2F3	Downregulated	(Fang et al. 2013)
miR-93	Suppression Of Wnt/B-Catenin Signaling Pathway	HDAC8 AND TRANSDUCIN	Down Regulated	(Yu et al. 2011)
miR-155	Induces TGF-Beta And EMT, Cell Invasion, and Migration	RHOA	Up Regulated	(Kong et al. 2008)
miR-429	Inhibition of EMT And Up-Regulation Ofe-Cadherin	ZEB1 AND ZEB2	Down Regulated	(Park et al. 2008)
miR-451	Reduction of Tumorigenicity and Self-Renewal	Macrophage Migration Inhibitory Factor	Down Regulated	(Bitrate et al. 2011)
miR-21	WNT Genes, Activation of WNT Signaling Pathway	TGF-BR2	Up Regulated	(Yu et al. 2012)
miR-145	Induction of Chemoresistance	Unknown	Up Regulated	(Yu et al. 2015)
miR-34a	Regulates Notch 1 Signaling	NOTCH1	Down Regulated	(Bu et al. 2013)
miR-140	Target MTX and 5-FU Resistance Phenotype	HDAC4	Up Regulated	(Song et al. 2009)
miR-215	Increases the Sensitivity to Tomudex and Methotrexate	Denticle less Protein Homolog (DTL)	Down Regulated	(Song et al. 2010)
miR-203	Activation of Snail Signaling	SNAIL	Up Regulated	(Ju et al. 2014)
miR-328	Inhibition of SP Cells And Chemo Sensitization	ABCG2 AND Matrix Metallopeptidase 16 (MMP16)	Down Regulated	(Xu et al. 2017)
miR-497	Sensitive to Cisplatin And 5-FU	Insulin-Like Growth Factor 1	Down Regulated	(Guo et al. 2013)
miR-125b	Activation of WNT Pathway	APC	Up Regulated	(Meyers et al. 2005)
miR-23a	Inhibition of Apoptosis	APAF1	Up Regulated	(Yu et al. 2015)
miR-10b	Inhibition of Apoptosis	BIM	Up Regulated	(Shang et al. 2014)
miR-425-5-p	Inhibition of Apoptosis	PDCD10	Up Regulated	(Zhang et al. 2016)
miR-587	Elevation of PI3K/AKT	PP2R1B/PP2A	Up Regulated	(Zhang et al. 2015a, b)
miR-23a	Elevation of MSI	ABCF1	Up Regulated	(Li et al. 2015)
miR-192	Enhanced Cell Cycle Progression	P21/P27	Down Regulated	(Boni et al. 2010)
miR-330	Enhanced Cell Growth	TS	Down Regulated	(Xu et al. 2017)
miR-494, -27a,-27b	Stimulation of 5-FU Catabolic Pathway	DPD	Down Regulated	(Offer et al. 2014)
miR-20a	Stimulation of Autophagy/Downregulation of Apoptosis	BNIP2	Down Regulated	(Chai et al. 2011)
miR-302a	Stimulation of Cell Survival and Development	ERK1/2 and AKT	Down Regulated	(Chen et al. 2019)
miR-122	Stimulation of Cellular Development and Glucose Metabolism	PMK2	Down Regulated	(He et al. 2014)
miR-34a	Elevation Level of Tumor Growth Rate	SIRT1, E2F, LDH	Down Regulated	(Li et al. 2015)
miR-519c	Inhibition of Drug Efflux Rate	ABCG2	Down Regulated	(To et al. 2015)
miR-143	Elevation of Apoptotic Cell Death Rate	ERK5, NF-κB, C-KIT, BCL2	Up Regulated	(Borralho et al. 2009)
miR-204	Decrease in cell development and differentiation	HMGA2, PI3K/AKT	Up Regulated	(Wu et al. 2016)
miR-365, -1915, -129, and-139-5 p	Increase in Apoptosis	BCL2	Up Regulated	(Li et al. 2016)
miR -218	Decrease Level of 5-FU Metabolism	TS	Up Regulated	(Ye and Weinberg 2015)
miR-22	Inhibition of Autophagy and Elevation of Apoptosis	BTG	Up Regulated	(Zhang et al. 2020b)

Abbreviation: *ABCG2*, ATP binding cassette subfamily G member 2; *ABCF1*, ATP binding cassette subfamily F member 1; *APC*, adenomatous polyposis coli; *BIM*, Bcl-2-like protein 11; *Bcl2*, B-cell lymphoma 2; *BTG1*, BTG antiproliferation factor 1; *BNIP2*, BCL2 interacting protein 2; *DPD*, dihydropyrimidine dehydrogenase; *E2F1*, E2F transcription factor 1; *HMGA2*, high-mobility group AT-hook 2; *LDH a*, lactate dehydrogenase A; *MSH2*, MutS protein homolog 2; *MMR*, mismatch repair; *MSI*, microsatellite instability; *NFκB*, nuclear factor-κB; *PMK2*, pyruvate kinase isozymes M1/M2; *PDCD10*, programmed cell death 10; *PPP2CA*, protein phosphatase 2 catalytic subunit α; *SIRT1*, sirtuin 1; *TS*, thymidylate synthase; *CSC*, Cancer stem cell; *EMT*, Epithelial to mesenchymal transition; *MTX*, Methotrexate

is a characteristic of the epithelial-mesenchymal transition (EMT) (Hills et al. 2012), including loss of E-cadherin, and increased mesenchymal markers like vimentin and fibronectin. Genetic variables and promoter repression, such as Twist, Slug, Zeb1, Zeb2, and Snail, suppress E-cadherin promotion (Serrano-Gomez et al. 2016).

The Warburg effect, first identified in 1924, demonstrates that cancer cells use glycolysis to generate ATP, nucleotides, lipids, and amino acids for cell proliferation. It also plays a role in tumor microenvironment shifts, activating oncogenes like PI3K and HIF-1α (Upadhyay et al. 2013). The majority of tumor beds experience increased oxygen demand and hypoxia as a result of hypoxic cancer cells' effective absorption of glucose, pyruvate metabolism to lactate, activation of resistance genes, and induction of chemoresistance (Eales et al. 2016; Seebacher et al. 2021). Acidosis and hypoxia induce chemoresistance by upregulating fatty acid synthase expression and lipid metabolism (Singh et al. 2023). Aerobic glycolysis in cancer cells generates lactate, allowing them to export lactate via MCTs, maintaining intracellular acid-base balance. Cancer cells exhibit a distinct pH gradient, with intracellular pH being more alkaline and extracellular pH being more acidic (Bogdanov et al. 2022). The immunological response is inhibited by lactate in various ways:

- The cytotoxicity of perforin and granzyme is directly inhibited by lactate.
- High amounts of extracellular lactate in T cells cause endogenous lactate to build up and inhibit the release of pro-inflammatory cytokines.
- Natural killer (NK) cell function is indirectly weakened by lactate's recruitment of monocyte-derived dendritic cells (Liu et al. 2021).

It is well known that acid-activated proteases increase the motility of cancer cells (Mahoney et al. 2003) and that the buildup of H+ and lactate in the TME inhibits the production of cytokines by a variety of immune cell types (Wang et al. 2021b). It has been noted that glutamine metabolism is favored over glucose metabolism in cancer cells maintained at pH 6.5, which reduces the rate of H+ production from glycolysis (Chiche et al. 2010). Fatty acid metabolism is dramatically altered by ambient acidosis, with FA oxidation (FAO) serving as the main source of acetyl-CoA needed to sustain the TCA cycle (Corbet et al. 2020). Extracellular acidosis causes weakly basic drugs like vincristine and paclitaxel to be neutralized and protonated, preventing them from crossing the cytomembrane and losing effectiveness. They are segregated into acidic lysosomal vesicles, and due to intracellular alkalinity, they become ineffective before reaching their target, referred to as the "ion trapping mechanism"(Liu et al. 2021).The ABCB2 transporter and internal acidic vesicles, P-gp, facilitate drug removal from cancer cells via extracellular acidosis, thereby enhancing chemoresistance (Liu 2019; Liu et al. 2021). Through paracrine signaling, stromal cells aid in invasion, metabolism, metastasis, and chemoresistance in cancer. The tumor microenvironment is formed by the invasion of immunosuppressive cells, where CAFs and TAMs play prominent roles. In what is known as the "Reverse Warburg effect," as cancer spreads, cancer cells not only recruit glycolysis and glutaminolysis from nearby cells for their benefit as well as that of the neighboring cancer cells via MCT1 and MCT4, but they also encourage stromal cell differentiation into CAFs and TAMs to secure an edge in survival (Alfarouk et al. 2015). Curcumin is responsible for inhibiting MCT1 and reversing chemoresistance in hepatic cancer cells (Soni et al. 2020). For example, colon cancer favorably regulates the increase of integrin avβ1 expression in Transforming growth factor β (TGFβ) expression, which is required for EMT and serves as a signal for cancer cells to survive drug exposure. Such signals are transmitted through the interaction of integrin avβ1 with stromal cell adhesion molecules. Research indicates a relationship between EMT events and 5-FU resistance over time, with mesenchymal and epithelial markers such as TET1, vimentin, SNAIL, NF-κB p65 subunit, and NNKD2 being highly elevated in 5-FU-resistant cells (Liu 2009; Liu et al. 2013b; Parkin 2019). However, 5-FU-resistant colon cancer cells and the sera of patients with worse clinical outcomes showed significant expressions of the chemokine C-X-C motif ligand 13 (CXCL-13). However, some investigations have shown a direct correlation between Wnt/ β catenin signaling and the CXCL12/CXCR4 axis in improving 5-FU resistance. Chemokines such as CXCL-13 and CXCL-12 have the potential to attract T-regulatory cells to the microenvironment, hence promoting 5-FU tolerance (Yu et al. 2017; Zhang et al. 2020a). According to a study, the scaffold protein β-arrestin1 in CRC-CSCs decreases stem cell apoptosis and commences crosstalk between the β-catenin pathway and ET-1/ETAR signaling, potentially providing a different course of treatment for CRC patients (Fodde and Brabletz 2007; Cianfrocca et al. 2017). β-6 integrin is crucial for colorectal cancer cell invasion, metastasis, and ECM breakdown. After 5-FU treatment, overexpression of β-6 integrin protects cells from 5-FU's harmful effects by activating the ERK/MAPK pathway, upregulating Bcl2, and downregulating Bax (Liu et al. 2013b). It has been discovered that connexins, sometimes referred to as gap junctions, are a type of cell surface adhesion protein that reduces the effectiveness of 5-FU toxicity in CRC cells (Zou et al. 2016). New theories suggest that cell fusion, not just adhesion molecules, is crucial for cancer development, spread, and phenotypic diversification, with proteins like RhoA, radixin, GTP-binding protein a13, ADAM10, and myosin regulatory light chain playing roles.

Nectin-4 and small molecules

Nectins are important members of the IgSF family, along with nectin-like compounds (Chatterjee et al. 2021). With three extracellular loops that resemble immunoglobulins and a single transmembrane region, this family of cellular adhesion molecules has a similar structure and is important for the development and maintenance of tight junctions and adherences (Mandai et al. 2015; Cortés et al. 2023). The Cancer Genome Atlas (TCGA) revealed that Nectin-4 is primarily linked to the TNM stages of colorectal cancer, as assessed in 372 colorectal cancer samples (Chatterjee et al. 2021; Klekowski et al. 2023). Das et al.'s study highlights Nectin-4's role in 5-FU resistance and its significant influence on colorectal cancer cell development, proliferation, and migration. Cervix cancer cells, including cancer stem-like cells, exhibit resistance to 5-FU and increased Nectin-4 expression. Nectin-4, NOTCH signaling elements, and proteins associated with CSCs were expressed more often in a metastatic model derived from TS-positive 5-FU-resistant cervical cancer cells. Nectin-4 endo-domain nuclear translocation in hypoxic environments increases cell proliferative and invasive properties (Nayak et al. 2019). Small molecule inhibitors (SMIs) are being explored to combat 5-FU resistance, with most substances enhancing its cytotoxic effects. Individuals who express more ABC transporter may benefit from 5-FU therapy in conjunction with U-332, a uracil analog (Azwar et al. 2021). Bartucci et al. discovered that RU-A1 is a potential BMI1 inhibitor, making HCC cells more sensitive to 5-FU therapy, resulting in irreversible cell cycle arrest and stopping cell proliferation and migration in vitro (Bartucci et al. 2017). HDAC inhibitors, such as valproic acid and depsipeptide, enhance the anticancer effect of 5-FU in colon cancer by downregulating TYMS (Table 1), activating caspase-3/7, and modulating MHC class II gene expression (Okada et al. 2016). Small molecule inhibitors decitabine and quinacrine have been shown to reverse 5-FU in colon cancer cells by demethylating the TYMP promoter and improving Nrf2 degradation (Okada et al. 2016). The membrane-bound O-acyltransferase porcupine (PORCN) is essential for the secretion of Wnt ligands. A small PORCN inhibitor, ETC-159, has shown promise in preclinical studies of colorectal cancer with RSPO-translocated tumors. Phase I studies included ten patients with colorectal and renal cancer (Wang et al. 2013; Teneggi et al. 2016). Salinomycin, a small chemical LRP6 inhibitor, targets CSCs by suppressing Wnt signaling through LRP6 degradation. When XAV939 is used to block Wnt signaling in SW480 CRC cells, the Axin-GSK3β complex is increased. The novel tankyrase antagonists G007-LK and G244-LM reduce Wnt/β-catenin signaling by suppressing APC mutation-driven signaling. Pyrvinium increases the CK1α kinase activator by suppressing Wnt signaling and proliferation (Thorne et al. 2010; Lau et al. 2013; Fan et al. 2014; Lu and Li 2014).

Signaling pathways

Therapeutic resistance in colorectal cancer is associated with growth signaling pathways that are activated by markers such as PI3/AKT, Hedgehog, Notch, TGF-β, Wnt/-catenin, Hippo, and others (Chen and Sikic 2012). Blocking Notch signaling with DAPT inhibits cell proliferation and decreases chemo-resistant and ionosphere cells, suggesting Notch signaling may be essential for CSC persistence and cancer patients' resistance to conventional chemotherapeutics (Huang et al. 2015).GLI-1, a nuclear modulator of hedgehog signaling, is crucial for carcinogenesis and treatment resistance in colorectal cancer. Its knockdown reduces resistance, and the level of expression increases in colon cancer cells that are resistant to 5-FU (Palle et al. 2015). YAP1 signaling is linked to cell proliferation and metastasis in colorectal cancer. Treatment with 5-FU leads to reduced survival rates and higher cancer relapse risk. Increased expression of YAP target genes (Table 1) in 5-FU resistant cells makes them more susceptible to 5-FU therapy, both in vivo and in vitro through YAP1 knockdown (Wierzbicki and Rybarczyk 2015). PI3K/AKT in cancer cells leads to 5-FU resistance and CSC-like characteristics in MACC1, with MACC1 enhancing 5-FU-resistant cells and MACC1 knockdown decreasing MDR1 expression and increasing 5-FU sensitivity (Wang et al. 2017). A mutation in any one of the proteins in the Wnt/β-catenin signaling pathway, a well-known Wnt signaling cascade, is present in almost 94% of cases of colorectal cancer (Suraweera et al. 2006; Cancer Genome Atlas Network 2012). According to a recent study, 5-FU therapy in conjunction with curcumin efficiently inhibits the Wnt signaling pathway and EMT activity, which increases the rate of activation of 5-FU-triggered apoptosis in cells that are resistant to 5-FU (Lu et al. 2020). β-catenin stabilizes and transports HIF-1α in 5-FU resistance, with TCF1 interacting with the complex but not TCF4. High HIF-1α levels are linked to cellular translocation, stability, and transcription up-regulation in CRC. HIF-1α transcription and translation are upregulated by activated PI3K/Akt signaling, which is a significant factor in human cancer. Furthermore, HIF-1α is stabilized and trans-activated by the PI3K/Akt signal, independent of oxygen levels. Researchers found that when ROS levels rise, the PI3K/Akt signaling pathway makes HIF-1α levels rise in 5-FU-R cells. 5-FU-resistant CRC, PI3K/Akt signaling controlled HIF-1α mRNA and protein in response to an excess of ROS rather than oxygen levels (Yeh et al. 2018; Boso et al. 2019; Dong et al. 2022). Several drugs are ineffective against cancer cells because the ABCB1 gene has an NF-κB binding site, which

causes the gene's transcription to be elevated. Curcumin, a phytochemical, effectively inhibits NF-B's nuclear translocation, thereby reducing P-gp overexpression in drug-resistant cancer cells, a process that RTK, a small GTPase family, triggers. When Ras kinase binds to GTP and activates Raf kinase, MEK is phosphorylated and activated. MEK activates MAP kinase (MAPK), which controls cell survival and proliferation. In colorectal and NSCLC cells, acquired resistance has been linked to MEK activation. According to research by Eum et al., drug resistance in Ras-NIH 3T3/MDR cells can be reversed by downregulating ABCB1 expression through suppression of Raf/MEK/ERK signaling (Lopes-Rodrigues et al. 2016; Martinelli et al. 2017).

Chemosensitizers

Flavonoids, found in plants and animals, are a common polyphenolic component in human diets. They have natural P-gp inhibitory and antineoplastic properties, and when combined with 5-fluorouracil, they may synergistically affect cancer prevention as shown in Fig. 2 (Kandaswami et al. 2005). Flavonoids, found in the colon, are absorbed by cancer cells while in the digestive tract, killing them and preventing their proliferation. They offer greater safety, efficacy, and economy compared to chemical or synthetic inhibitors (Kuppusamy et al. 2014). These phytochemicals are often known as chemosensitizers. Multidrug

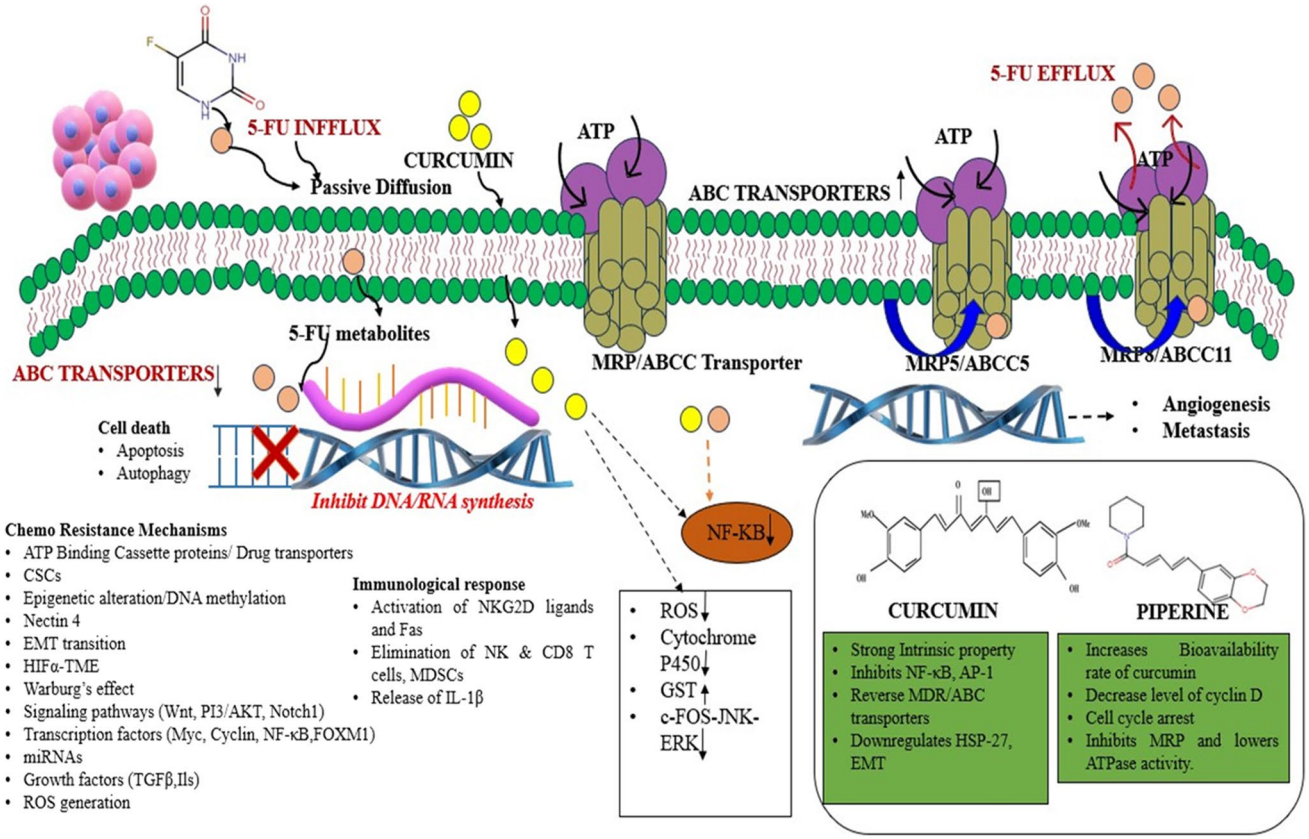

Fig. 2 5-Fluorouracil facilitates through passive diffusion across the surface of a cell and inhibits the RNA/DNA synthesis by incorporating themselves with the enzyme thymidylate synthase. However, presence and overexpression of ATP binding cassette proteins in the surface pump out 5-FU through ATP hydrolysis leading to conformational change of the membrane. MRP5/ABCC5 and MRP8/ABCC11 are responsible for 5-FU resistance mechanism. Various resistance mechanisms are involved with respect to 5-FU chemoresistance which include CSCs, EMT transition, TME, Nectin 4, Small molecules, Wnt signaling pathway, growth factors, miRNAs etc. Co-treatment with curcumin and piperine will enable to avoid the efflux of 5-FU through the cell as curcumin will downregulate NF-κB, cytochrome P450, ROS, JNK_ERK pathways etc. Piperine enhances curcumin bioavailability and cell residence time, initiates cell cycle arrest, and binds to the walker region of the transmembrane domain, reducing ATPase activity. CSCs—Cancer Stem Cells, MRP—Multidrug Resistance-Associated Protein, ABCC—ATP-Binding Cassette Subfamily C, HIF—Hypoxia-Inducible Factor, TME—Tumor Microenvironment, EMT—Epithelial-Mesenchymal Transition, ROS—Reactive Oxygen Species, PI3/AKT—Phosphatidylinositol 3-Kinase/Protein Kinase B (Akt), NOTCH1—Neurogenic Locus Notch Homolog Protein 1, FOXM1—Forkhead Box M1, TGFB—Transforming Growth Factor Beta, GST—Glutathione S-Transferase, CFOS-JNK—c-Fos c-Jun N-Terminal Kinase, ERK—Extracellular Signal-Regulated Kinase

resistance chemosensitizers have two main modes of action:

a) they can change the expression or
b) activity of the MDR protein.

The search for chemosensitizers that block drug transporter function and hence reverse MDR has gained momentum alongside biochemical and clinical studies examining the underlying mechanisms and regulation of these proteins. Depending on how the drugs work on the specific transporter proteins, they can be grouped into several categories that block MDR. These agents may be efficiently carried by the pumps, or they may not be transported at all by the pumps because of the high affinity of the transporter on their drug-binding domains compared to any cytotoxic drugs. In the former scenario, the MDR tumor cell's ATP consumption may rise significantly in response to activation of the pump turnover. The tumor cells may become advantageously and collaterally sensitive to the modifying drug as a result. In the latter scenario (which most likely applies to PSC833), a substrate analog that is impermeable to pumping locks down the transporter, preventing it from being released from the binding sites (al-Shawi et al 1994; Sikic 1997). Drug analogs that either noncompetitively or competitively prevent drug efflux either through MDR1 or MRP are included in the first category. MDR chemosensitizers can prevent ATP binding or utilization in drug pumps by covalent or nonhydrolyzable interactions with essential amino acids, as in the cases of azido-ATP and NBD chloride. It is certainly unrealistic to anticipate such chemicals to have any specificity against MDR since they will also affect most ATP-binding proteins, such as protein kinases and ion pumps. Antibodies that hinder drug transporter function fall within the third class of MDR chemosensitizers(Ambudkar 1995; Limtrakul 2007). Numerous monoclonal antibodies have been shown to react with the cytoplasmic functional regions of MDR1 or MRP; because these antibodies do not penetrate tumor cells, their in vivo applicability has not been explored. All other potential drug pump antagonists that are difficult to distinguish based on their mode of action would fall into the final category of MDR chemosensitizers. With minimal selectivity, several detergents appear to block MDR pumps within the hydrophobic interactions or closer to the lipid bilayer. Naturally occurring substances, especially phytochemicals, and their synthesized conjugates have been thoroughly studied for their potential therapeutic effects in cancer prevention and treatment, in addition to their significance in chemo-sensitization towards malignant cells to overcome MDR. One such phytochemical that has been thoroughly researched is curcumin. It is known to sensitize cancer medications in MDR malignancies and targets a variety of tumors. Due to its poor water solubility and rapid metabolism, the compound's clinical application is restricted even though pre-clinical tests revealed promising potential. To get around this, several curcumin analogs have been created and put through preclinical testing to find stronger therapeutic effects (Dandawate et al. 2012; Vyas et al. 2013). Curcumin has a hydrophobic nature, while 5-fluorouracil has a hydrophilic tendency. Due to the poor absorption, metabolism, and elimination of both 5-fluorouracil and curcumin, conjugation of these two drugs is almost impossible. Only 10–20% of 5-fluorouracil is bioavailable. When piperine and curcumin are used together to boost bioavailability, these problems can be resolved (Fig. 2). It is necessary to actively search for a chemo-sensitizer to reverse the resistance mechanism and enhance treatment efficacy by improving the patient's quality of life.

Curcumin

Curcumin (CUR, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), a diarylheptanoid found in Zingiberaceae plants like Curcuma longa, C. zedoaria, and C. wenyujin, is a promising phytocompound found in their rhizomes. Curcumin, a highly pleiotropic molecule, has been identified as a significant therapeutic agent against colorectal, breast, and cervical cancer, acting as a modulator for signaling pathways controlling cellular growth metabolism, apoptosis, and inflammation(Noorafshan and Ashkani-Esfahani 2013). Curcumin's hydrophobic nature allows it to penetrate the plasma membrane and spread across the endoplasmic reticulum and nuclear envelope, causing structural and functional changes in the cell membrane (Jaruga et al. 1998). Curcumin exposure increased plasma membrane permeability in cells, but decreased mitochondrial membrane potential, phosphatidylserine exposure, and cell shrinkage (Jaruga et al. 1998). Curcumin is a bis-α, β-unsaturated β-diketone that displays keto-enol tautomerism, exhibiting an intact enol form in alkaline media and a keto form in neutral conditions. Its restricted use is due to diketone fragment instability and the presence of a 63-methylene group. Curcumin composition includes 77% diferuloylmethane, 17% dimethoxy curcumin, and 6% bisdemethoxycurcumin curcumin, which can be divided into various metabolites like curcumin glucuronide, dihydro curcumin, and ferulic acid (Anand et al. 2007). Curcumin's low bioavailability and selectivity are due to its poor absorption, high metabolism rate, limited tissue distribution, low serum levels, and short half-life, yet it shows strong intrinsic activity. To address issues with curcumin metabolism and liver glucuronidation, combinatorial compounds, adjuvants like piperine, nanoparticles, liposomes, micelles, phospholipid complexes, derivatives, and analogs can be used, enhancing absorption rates and chelation with metals (Anand et al. 2007; Maiti et al. 2007). A recent study found that curcumin, when replaced with an

α, β-unsaturated ketone and asymmetrically replaced with phenyls and aromatic compounds, mimics various antiangiogenic activities, demonstrating the need for significant chemical modification (Woo et al. 2005). Curcumin inhibits carcinogenesis, suppresses it, and reverses it, with strong anti-inflammatory, anti-fungal, anti-viral, and anti-clastogenic properties as shown in Fig. 3 (Joe et al. 2004). Antioxidant agents protect cancer by reducing excessive levels of reactive oxygen species (ROS), as evidenced by the expression of the catalase enzyme in malignant cells. This leads to normal growth, normalized growth rate, and reduced tumor production in athymic mice, indicating ROS's significant role in carcinogenesis (Arnold et al. 2001). Curcumin may prevent cancer by inhibiting Phase I enzymes like CYP and activating Phase II enzymes like GST, which are crucial for activating and detoxifying carcinogens. According to current research, curcumin can activate GST and inhibit cytochromes P450 in vivo (Danielson 2002). Curcumin has been shown to decrease cellular ROS levels in in-vivo, which in turn activates NF-κB, as demonstrated by numerous studies. This implies that curcumin may lower cellular ROS levels and hence inhibit NF-κB activation in vivo (Gloire et al. 2006). Low glutathione S-transferase P1-1 levels are the result of curcumin's inhibition of VEGF and angiopoietin 1 and 2 in EAT cells, NIH 3T3 cells, and VEGF receptor-2 in HUVEC cells. This inhibition causes apoptosis in a variety of cell lines including, scleroderma lung fibroblasts, without damaging normal lung fibroblasts (Duvoix et al. 2005). According to Bush et al., curcumin causes caspases 8 and 9, while p53 stays unaltered. Nevertheless, Fas triggers the death receptor pathway independently of the ligand. Anto et al. overexpressed these two essential proteins, which prevented curcumin-induced apoptosis, so far confirming the function of Bcl-2 and Bcl-XL inhibition (Fig. 3). Curcumin prevents the activation of NF-kB and AP-1, two key transcription factors, and significantly inhibits NF-κB and AP-1 in K562 leukemia cells induced by tumor necrosis factor and TPA binding to target sequences (Bush et al. 2001; Shao et al. 2002). NF-κB suppression results from IkB kinase (IKK) complex inhibition, which prevents NF-κB p65 translocation and IkBα phosphorylation. Several groups verified these findings and reported that curcumin prevents NF-κB activation induced by lipopolysaccharide (LPS), thrombin, TNFα, TPA, and interleukin (IL-1). Given that most anticancer drugs, including doxorubicin, cause upregulation of NF-κB, resulting in the development of drug resistance, this

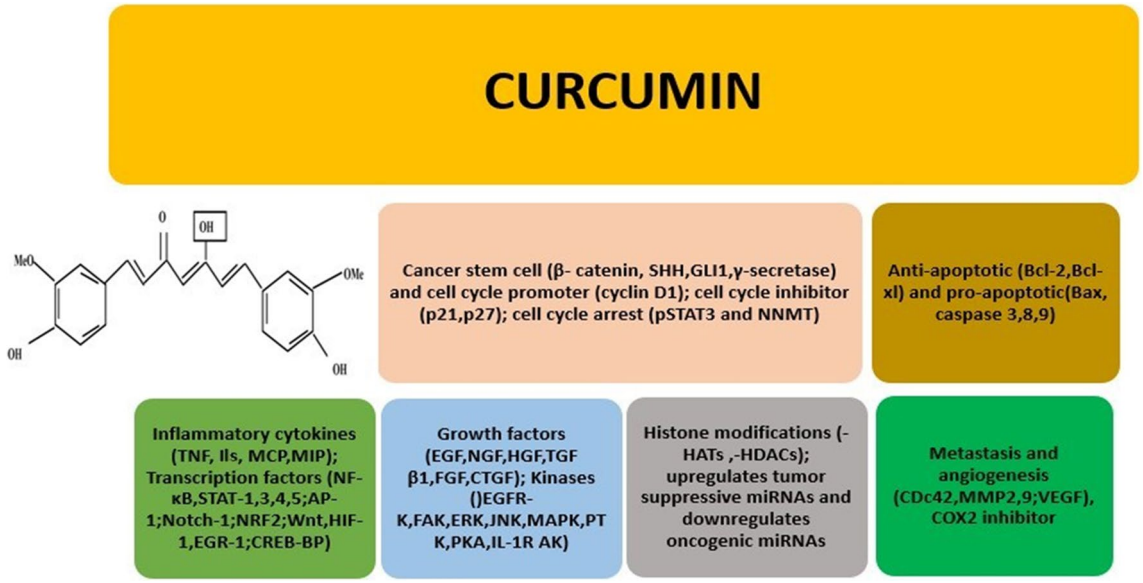

Fig. 3 Molecular targets of curcumin that target multiple signaling pathways involved in inflammation, cell proliferation, and apoptosis. Additionally, it has been found to modulate the activity of various enzymes and transcription factors that play a role in cancer progression and development. SHH—Sonic Hedgehog, GLI2—GLI Family Zinc Finger 2, PSTAT3—Phosphorylated Signal Transducer and Activator of Transcription 3, NNMT—Nicotinamide N-Methyltransferase, BCL2—B-Cell Lymphoma 2, BCL-XL—B-Cell Lymphoma Extra Large, TNF—Tumor Necrosis Factor, IL-S—Interleukin-Subtype, MCP—Monocyte Chemoattractant Protein, MIP—Macrophage Inflammatory Protein, STAT—Signal Transducer and Activator of Transcription, AP-1—Activator Protein 1, NRF2—Nuclear Factor Erythroid 2-Related Factor 2, HIF1—Hypoxia-Inducible Factor 1, EGR1—Early Growth Response Protein 1, CCEB-BP—CCAAT/Enhancer-Binding Protein Beta Binding Protein, EGF—Epidermal Growth Factor, NGF—Nerve Growth Factor, HGF—Hepatocyte Growth Factor, TGF—Transforming Growth Factor, FGF—Fibroblast Growth Factor, CTGF—Connective Tissue Growth Factor, EGFARK—Epidermal Growth Factor Receptor Kinase, FAK—Focal Adhesion Kinase, ERK—Extracellular Signal-Regulated Kinase, JNK—c-Jun N-Terminal Kinase, MAPK—Mitogen-activated protein Kinase, PTK—Protein Tyrosine Kinase, PKA—Protein Kinase A, IL-1—Interleukin 1, HATs—Histone Acetyltransferases, HDACs—Histone Deacetylases

inhibitory action should be considered to optimize chemotherapy treatment. Curcumin prevents NF-κB from binding to DNA and inhibits JNK and ERK, which stops c-Fos transcription factor activation and stops IKK activation, IkBα phosphorylation, and NF-κB p65 translocation. Curcumin impacts the Janus Kinase-Signal Transducer and Activator (JAK/STAT) pathway and activates the heme-oxygenase (HO)-1 pathway in kidney epithelial cells by activating the Nrf2/antioxidant response element (ARE) pathway (Chan et al. 2003; Chearwae et al. 2006; Bhatt et al. 2010). According to human clinical trials, the chemical is pharmacologically safe at doses up to 10 g/day with no dose-limiting effects (Limtrakul 2007). According to a recent study, curcumin I, desmethoxycurcumin II, and bisdemethoxycurcumin III are the most effective chemosensitizers of MRP1, Pgp, and MXR. One of the main metabolites of curcumin, THC, also prolongs MDR-reversing activity (Chearwae et al. 2006; Limtrakul 2007). Curcumin's biological and pharmacological benefits, cyclicity, lipophilicity, and toxicity led to an investigation into potential interactions with Pgp expression and function. Curcumin increased rhodamine 123 accumulation (1–55 μM) and prevented its efflux from drug-sensitive KB-3-1 cells, but not in wild-type cells. Curcumin's brief exposure time (1–2 h) suggests it may not reduce MDR1 gene expression, reducing Pgp levels. Curcuminoids decrease ABCG2-mediated drug resistance by interacting with drug transporters at high-affinity binding sites (Chearwae et al. 2006; Mori et al. 2006). Curcuminoids, particularly curcumin I, effectively reduce ABCG2-mediated drug resistance by interacting with drug transporters at substrate-binding sites, with curcumin I being the most effective pure curcumin in this regard. Curcumin downregulates DNA damage-responsive genes in cancer cells, including ATM, ATR, BRCA1, and MGMT. When compared to 5-FU alone, the combination of curcumin and 5-FU dramatically increases the rate of cell death in breast carcinoma cells and chemo-sensitive cells. Repetitive 5-FU injection increases thymidylate synthase (TS) expression, activating NF-κB and making breast cancer cells resistant. Combining 5-FU and curcumin reduces TS and deactivates NF-κB, enhancing 5-FU therapeutic benefits and increasing colon cell sensitivity as shown in Table 3. Curcumin inhibits P-gp and MDR, increasing colon cell sensitivity to 5-FU, as shown in Table 3. ABC transporters release the drug, reducing its efficacy. Curcumin increases the toxicity of medications in colon cancer cells by suppressing P-gp, MRP1, and BCRP.

Table 3 Role of curcumin in colorectal cancer and its synergistic effect with 5-FU in CRC

FACTORS/ EXPRESSION	FUNCTIONS	REFERENCES
COX2	Inhibition of COX2 which plays the role of tumorigenesis of CRC in n heterozygous ApcD716 knockout mice	(Hsu et al. 2000)
COX2 (downregulated)	The synergistic effect when combined with 5-FU in HT29 cells	(Du et al. 2006)
COX-2 and cyclin-D1 (downregulation)	Conjunction with FOLFOX significantly improved HCT-116 and HT-29 cells' ability to suppress cell proliferation; and activation of EGFR, HER-2, IGF-1R, and AKT in chemo-surviving cells	(Do et al. 2013)
EMT (suppression)	Inhibition of cell proliferation and apoptosis in parental and 5-FU resistant cell lines expressing the chemo-sensitizing effect	(Toden et al. 2015)
NF-κB (downregulated)	Decreased the levels of proliferative (cyclin D1) and anti-apoptotic (Bcl-xL) proteins and increased the cleavage of pro-apoptotic proteins (caspases 8, 9, and 3, PARP, and Bax)	(Shakibaei et al. 2013, 2014)
NF- κB /PI-3 K/Src pathway	Inhibited IKK activation and IκBα phosphorylation, downregulating this activation to reverse MDR of 5-FU	(Shakibaei et al. 2015)
MDR (downregulated)	Reduced the expression level of MRP1 and p-gp in human-resistant CRC	(Lu et al. 2020)
HSP-27, p-gp (downregulated)	Reverse MDR in HCT-8	(He et al. 2019)
NRF-2	Apoptosis; inhibited the production of the ratio of Bcl-2/Bax; MDR of HCT-8/5-Fu cells was reversed	(Zhang et al.2018)
Survivin, BCL2, HSP27, p-gp	Reverse MDR in HCT8	(Fang et al. 2013)
MACC1	Curcumin controls the PI3K/AKT/mTOR pathway	(Ma et al. 2022)
EMT (reverse)	Inhibition of WNT pathway in HCT116 cells	(Lu et al. 2020)
COX2	Decrease in COX2 protein expression	(Du et al. 2006)
miRNA	Supresses EMT and PRC in CRCs	(Toden et al. 2015)

Abbreviations: *EGFR,* Epidermal Growth Factor Receptor; *HER-2,* Human Epidermal Growth Factor Receptor 2; *AKT,* Protein kinase B (also known as Akt); *EMT*, Epithelial-Mesenchymal Transition; *NRF2,* Nuclear factor erythroid 2-related factor 2; *MACC1,* Metastasis Associated in Colon Cancer 1; *HSP-27,* Heat Shock Protein 27; *IGF-1R,* Insulin-like Growth Factor 1 Receptor; *PRC,* Polycomb Repressive Complex; *IKK,* IκB Kinase

Curcumin effectively eliminates 5-FU resistance in HCT-8 cells by downregulating P-gp and HSP-27, inducing apoptosis through survivin and Bcl-2 expression, and decreasing 5-FU resistance in resistant MMR defective cells (Shakibaei et al. 2014; Keyvani-Ghamsari et al. 2020). P-gp, expressed in the intestinal tract, regulates drug delivery and absorption by reducing substrate uptake, preventing therapeutic plasma concentration and bioavailability. However, drug reduction can affect these concentrations. Transfer of the substrate, bound by ATP, occurs via cytoplasmic opening or membrane entrance to P-gp. ATP hydrolysis changes the substrate, requiring removal from the cell. Phosphate is separated from the original ATP molecule, releasing substrate. By releasing adenosine diphosphate (ADP), curcumin inhibits P-gp function. This reactivates the process by enabling a new ATP molecule to attach to the secondary ATP binding site (Kodan et al. 2021).

Early identification of CRC disease, often at stage III or IV, is crucial for effective treatment, as it makes it difficult to administer the necessary treatment. The enhanced permeability and retention (EPR) effect in tumors occurs due to vascular epithelium disruption, increasing the gap between cells. Passive targeting uses this effect to create nanoparticles (NPs) that can infiltrate tumors by traversing these intercellular gaps. Encapsulating pharmaceuticals in a carrier system made of polymers can enhance therapeutic outcomes by shielding molecules, reducing nonselective exposure, and improving the duration of drug presence in the bloodstream (Sadeghi-Abandansari et al. 2021). The surface charge of nanoparticles significantly influences cancer cell absorption. Positively charged nanoparticles are highly absorbed by tumor cells but generate significant immunological responses, making neutral or negatively charged nanoparticles preferred in therapeutic settings (Masloub et al. 2016). Combination chemotherapy could also benefit from nanoparticulate delivery, allowing for the combination of hydrophobic and hydrophilic drugs such as 5-FU and curcumin, controlled drug release, and drug loading ratio adjustments. Curcumin's limited bioavailability and suboptimal pharmacokinetics can be addressed by using delivery vehicles and producing curcumin derivatives. Effective delivery systems should enhance curcumin's potency and toxicity without adverse effects on healthy cells. Liposomes, composed of two phospholipid bilayers, serve as a delivery mechanism for curcumin, enhancing its stability, absorption in the gastrointestinal tract, and plasma concentration. These nano-based delivery groups can be explored to address the issue of curcumin's suboptimal pharmacokinetics (Keyvani-Ghamsari et al. 2020). Polylactic-co-glycolic acid (PLGA) is a widely used polymer for encapsulating curcumin, which has been shown to trigger apoptosis in CRC cells using aptamers. The study assessed the therapeutic efficacy of phytosomal curcumin when combined with conventional chemotherapy (5-fluorouracil) in cell systems and a mouse model of colitis-associated colon cancer, showing curcumin effectively inhibited cell proliferation and invasion (Naeimi et al. 2022). Studies show that curcumin-loaded PLGA nanoparticles (Cur-NPs) improve oral bioavailability of curcumin by increasing water solubility and permeability, and inhibiting P-gp mediated efflux. Cur-NPs-A Pgp, a formulation containing curcumin and linked to P-gp, is more attractive to drug-resistant cervical cancer cell line KB-V1, leading to increased absorption of curcumin and intensified toxicity due to overexpression of P-gp, which is linked to aggressive behaviors and multidrug resistance (Punfa et al. 2012). Integrating curcumin into micelles enhances cytotoxicity, causing greater apoptosis in melanoma cells. Studies show curcumin-loaded lipo-PEG PEI complexes increase curcumin accumulation in B16F10 cells and increase toxicity by up to 20-fold in resistant cells. Khorsandi et al. inserted curcumin into LDH nanohybrid to overcome drug resistance and improve curcumin efficacy in photodynamic therapy for breast cancer cells (Khorsandi et al. 2015). Anitha et al.'s study found that co-encapsulating 5-fluorouracil with CUR enhanced its efficacy by suppressing COX2 expression in colon cancer. The combined administration of CUR and 5-FU in N, O-CMC NPs significantly increased anticancer efficacy against HT29 cells (Wong et al. 2019). Curcumin used alone or in combination, is safe and effective in enhancing chemotherapy drug effectiveness by blocking the ABC efflux transporter. It hinders tumor formation by halting the cell cycle, triggering programmed cell death, suppressing protein production, impeding cell survival pathways, and regulating immunological responses. Xiao et al. developed cationic polymeric nanoparticles that transport camptothecin and curcumin, showing a significant synergistic effect. They also included hyaluronic acid (HA) to enhance colon cancer targeting. HA's strong attraction to CD-44 receptors enhances the internalization of HA-functionalized NPs into cells, allowing them to interact with CD44 receptors, enhancing their effectiveness. Xia et al. developed HA-CPT/CUR-NPs for colon cancer treatment. Ex vivo experiments showed increased penetration and accumulation of HA-functionalized nanoparticles in colon tumors. The combination of CPT and Cur showed significant synergistic effects, with an IC50 value of 0.7 μM in Colon-26 cells (Xiao et al. 2015; Batra et al. 2019). Anirudhan et al. developed a transdermal drug delivery system (TDDS) containing 5-fluorouracil and curcumin. The system uses β-Cyclodextrin to encapsulate CUR and aminated nano dextran to entrap 5-FU. The resulting formulation is coated with opposite-charged polysaccharides. Studies on HCT-116 human cancer cell lines showed a decrease in cell viability with increased formulation concentration (Anirudhan et al. 2017). Curcumin nanoparticles maintain the apoptotic and anticarcinogenic effects of free curcumin, focusing on multiple levels of control in

cellular development and the programmed cell death process (Masloub et al. 2016). Exposure to curcumin in lung cancer cells increases their susceptibility to anticancer medications. Many patients discontinue chemotherapy due to side effects, reducing survival rates in later stages. Combining curcumin with 5-FU could reduce the 5-FU dosage without compromising its effectiveness, thus enhancing treatment efficacy (Zheng et al. 2021). Discoveries suggest that incorporating curcumin with 5-FU therapy could enhance chemotherapy efficiency by protecting normal cells from decreased viability, enabling larger doses or longer treatment durations, especially for individuals with DPD deficits with severe cytotoxicity (Ferguson and Orlando 2015).

The development of non-site-specific combination nanoparticulate formulations faces challenges due to off-site effects on healthy cells. Advancements in chemotherapeutic nano-formulations, incorporating antigens like folate, aim to improve the targeting of cytotoxic medications to tumor cells. Pharmaceuticals face challenges in transforming curcumin into a stable derivative with enhanced drug-like qualities. A poly (curcumin-dithiodipropionic acid) PCDA coating on nanoparticles was used to achieve this. The coating, composed of mono curcumin linked by disulfide bonds, breaks down when exposed to higher glutathione concentrations, releasing curcumin in response. Additional sophisticated techniques such as the prodrug method, polymer coating, complexation, and co-crystallization of curcumin necessitate significant investments of time and money, which are commonly considered drawbacks for pharmaceutical businesses (Batra et al. 2019). Researchers have developed nano-formulation medications targeting cancer stem cells (CSCs) to overcome drug resistance, especially in cells resistant to 5-FU. These drugs target surface markers and signaling pathways, with nanostructures made of organic and inorganic materials equipped with specific targeting ligands. Nanomaterials like liposomes, NLCs, NPs, gold nano-shells, dendrimers, carbon nanotubes, and cyclodextrin are being designed to improve cancer treatment effectiveness due to their biocompatibility, non-toxicity, and biodegradability (Sethy and Kundu 2021).

Piperine

Piperine, which is obtained from *P. longum* and *Piper nigrum*, is a chemical with enormous potential for its use as a bioenhancer. In addition to its anti-tumoricidal properties, piperine also makes cancer cells more susceptible to the effects of current chemotherapeutic treatments. Scientific evidence has now conclusively shown that piperine is responsible for pepper's capacity to increase bioavailability. Piperine has been demonstrated to enhance the bioavailability of various drugs and medications, including curcumin, in clinical trials (chemoprevention and other therapeutic effects) (Kumar et al. 2018). Piperine content ranges from 1 to 2% in long pepper and 5% to 10% in black pepper. Piperine is a yellow, crystalline substance with a specific gravity of 285.33 g/mol and a melting point between 128 and 130 °C. It dissolves weakly in water (1 g/25 L), although it is quite soluble in ether (1 g/1.7 mL) and alcohol (1 g/15 mL). It is a weak base that, in the presence of water, forms salts with strong acids that hydrolyze quickly. When hydrolyzed with an alkali, it produces an acid and a base (Sachan et al. 2021). Piperine is categorized structurally into three areas: the piperidine ring, the aliphatic chain, and the aromatic ring moiety. The chemical structure of piperine is made up of a (E, E)-diene chain and an amide bond that joins a benzo dioxo moiety to a piperidine ring (Rügheimer 1882; Geisler and Gross 1990; Afreen et al. 2021). The secondary metabolite piperine is produced by biosynthesizing its precursors, cinnamoyl-CoA and L-lysine. L-lysine undergoes decarboxylation to cadaverine and diamine with copper amine oxidase to form 5-amino pentanal, which is again converted into Δ1-piperidine Schiff base and further reduced to piperidine. Piperonyl-CoA is usually produced from a cinnamoyl-CoA precursor through a Claisen-like reaction involving chain elongation with malonyl-CoA. Ultimately, piperine is created when piperidine and piperonyl-CoA combine(Chavarria et al. 2016). Piperonyl chloride was the first chemical catalyst used to create piperine from piperidine. Piperine selectively targets and halts the cell cycle, inhibiting tumor growth and spread and causing cell cycle arrest in colon cancer by lowering cyclin D levels. Furthermore, piperine-associated elevation of p21Cip1 and p27Kip1 expressions was noted in cell lines related to prostate and colon cancer. Several studies indicate that piperine can inhibit apoptosis through several mechanisms. Early research on testicular germ cells showed that piperine had a concentration-dependent effect on the proteins Fas and caspase-3 and that piperine-mediated increased oxidative stress was the key cause. Triple-negative and HER-overexpressing colon cancer cells have been found to have a reduced ability to proliferate when piperine reduces Akt phosphorylation (Yaffe et al. 2015). Piperine and curcumin have been found to enhance disease prevention strategies related to ROS (Fig. 4) and related species (Panahi et al. 2015). A recent study in healthy individuals examined the potential synergistic effects of piperine and curcuminoid supplementation over 8 weeks. The combination of piperine (10 mg/day) and curcuminoids (1 g/day) significantly enhanced antioxidant status, reduced MDA and CRP levels, and improved serum SOD activities compared to a placebo. According to trial results, piperine increased curcuminoids' potency and bioavailability (Suresh and Srinivasan 2006; Salzedas et al. 2020). Piperine significantly reduces the activity of NADPH-cytochrome c reductase, UDP-glucuronyl transferase (UGT), and liver microsomal aryl hydroxylase.

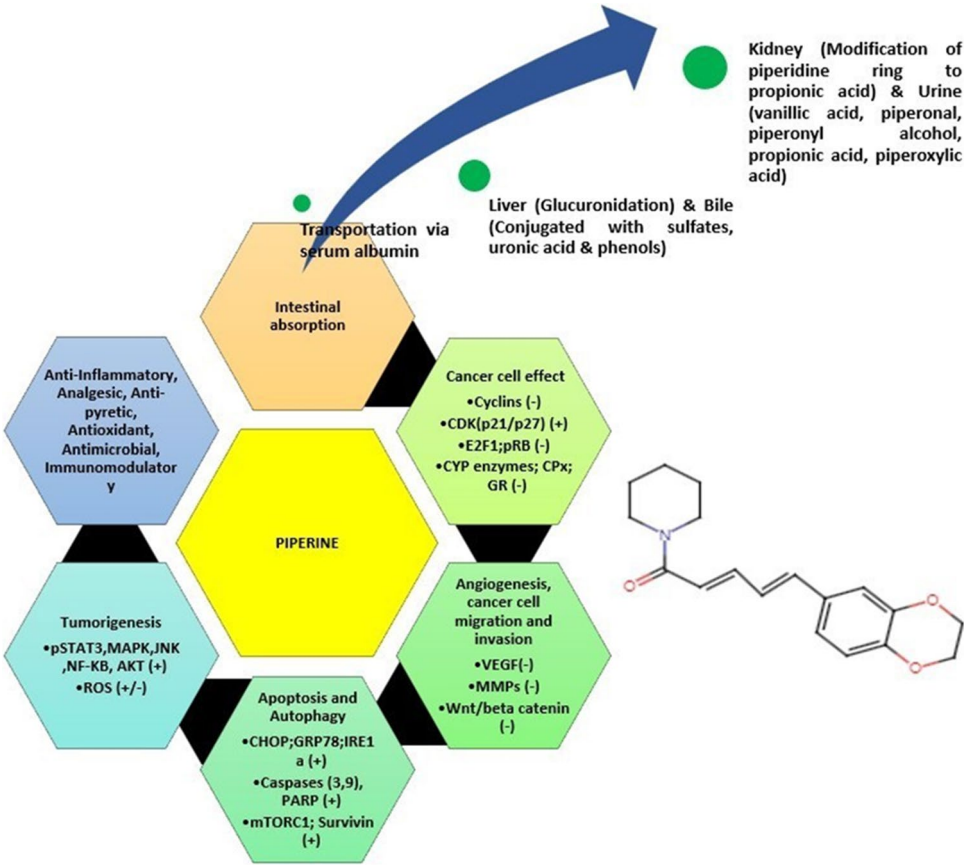

Fig. 4 A schematic diagram of piperine shows its absorption and metabolism and its molecular targets. Piperine suppresses the expression of cyclins, CDK, and other cell cycle molecular regulators (such as E2F1, and pRb) and impedes the growth of cancer cells. By inhibiting the VEGF/VEGFR signal pathway and MMPs, piperine has anti-migratory, anti-invasive, and anti-metastatic properties. Additionally, piperine's anticancer properties enable it to eliminate carcinogenesis through the inhibition of oncogenic proteins (such as JNK, p-STAT-3, and Akt) and disruption of the ROS signal pathway and influences the expression and functions of relevant proteins and signals, piperine specifically causes tumor cell death (apoptosis and autophagy). pSTAT3—Phosphorylated Signal Transducer and Activator of Transcription 3, MAPK—Mitogen-Activated Protein Kinase, INK—Inhibitor of Kinase, AKT—Protein Kinase B, ROS—Reactive Oxygen Species, CHOP—C/EBP Homologous Protein, GRP78—Glucose-Regulated Protein 78, IRE1—Inositol-Requiring Enzyme 1, PARP—Poly(ADP-Ribose) Polymerase, mTORC—Mammalian Target of Rapamycin Complex, VEGF—Vascular Endothelial Growth Factor, MMP1—Matrix Metalloproteinase 1, CDK—Cyclin-Dependent Kinase, E2F1—E2F Transcription Factor 1

MDR1, ABCC1, and ABCG2, which encode P-gp, MRP1, and BCRP, respectively, are inhibited by piperine in the long term. The study suggests that similar transcription factors, which are subsequently influenced by piperine, regulate the expression of all these drug transporters. Different transporters had different piperine inhibitory efficiencies and reversal ratios, which suggests that their substrate affinities varied. As a result, piperine functions as a broad-spectrum inhibitor of different drug transporters, making it a potentially useful tactic to enhance chemotherapy results. Concerning 5-fluorouracil, piperine inhibits the mechanistic action of the enzyme thymidylate synthase irreversibly. When co-administered with 5-FU, piperine decreases the half-life of the drug, helps with increased cytotoxicity and drug sensitization, improves suppression of the growth of the tumor, and reverses the side effects related to chemotherapy (Srinivasan 2007; Han 2011; Li et al. 2011). A study suggests that pepper, a popular spice, may down-regulate P-gp, MRP1, and BCRP, potentially increasing drug penetration into inaccessible organs like the testis, brain, and fetus, as it is located at the apical membrane of various organs (Li et al. 2011). Piperine inhibits MMP-9 as shown in Fig. 4 expression by regulating NF-κB/AP-1 and PKCα/ERK ½ activity, as reported in a study (Kumar et al. 2018). Research indicates that piperine may alter signaling networks involved in the epithelial-to-mesenchymal transition, thereby regulating intratumor heterogeneity, metastasis, and self-renewal in cancer stem cells (Warrier et al. 2022). According to a study, piperine successfully reduces the expression of MMP-9, which stops cell migration by blocking the pathways that activate AP-1,

NF-κB, ERK1/2, p38 MAPK, and Akt (Rather and Bhagat 2018). Piperine has been found to inhibit cancer growth by targeting DNA regions in the human G-quadruplex, a four-stranded structure produced during DNA metabolism.These structures are essential for controlling cellular activities that may be linked to the development of cancer. Piperine exhibits a strong binding affinity towards G-quadruplex DNA, namely the G-quadruplex structure that is generated at the CMYC promoter region. For tumors with abnormalities in DNA metabolism, piperine is a powerful chemo-preventive drug because of its capacity to bind G-quadruplex complexes (Tawani et al. 2016). There are several ways in which piperine-mediated redox alterations might affect cellular physiology; these effects can be dose-dependent, tissue- or cell-specific. As a result, depending on the circumstances, piperine can either encourage cell survival or cause cell death. By squelching free radicals, reactive oxygen species, and reactive metabolic intermediates, piperine, a naturally occurring antioxidant, efficiently guards against oxidative stress-mediated cellular damage (Srinivasan 2007; Yaffe et al. 2015). By downregulating cyclins D1 and D3, CDK4 and CDK6, preventing retinoblastoma protein phosphorylation, and activating p21 and p27, piperine suppresses HT-29 colon cancer cells in the G1 phase (Khan et al. 2022). Piperine regulates key proteins in the signaling network including secreted frizzled-related protein 2 (sFRP2), DKK-1, cyclin-dependent kinase 6 (CDK6), and B cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1), ensuring cell balance between dividing and quiescent states (Kim et al. 2012; Rather and Bhagat 2018). Piperine effectively inhibits the negative regulator of autophagy, mTOR, by inhibiting mTORC1 in HT-29 and Caco-2 cells. Piperine inhibits mTORC1 in HT-29 and Caco-2 cells, promoting autophagy, triggering pro-apoptotic ER stress components, and suppressing survivin expression and Akt activation (Moreau and Kaur 2017). Piperine has been reported to impact the tumor microenvironment, suggesting potential use in cancer treatment or prevention. Piperine, a potent inhibitor of MRP-1 and P-gp, interacts with the Walker A/P and Walker C loops for ATP-coupled efflux. Recently synthesized low molecular weight piperine analogs, Pip1 and Pip2, interact more favorably with P-gp due to competition with the ATP binding site. When paired with particular drugs such as vincristine, colchicine, or paclitaxel, both analogs show the ability to reverse drug resistance in P-gp overexpressing KB and SW480 cancer cells (Singh et al. 2013; Manayi et al. 2019). Piperine is a potent bioavailability enhancer for various chemotherapeutic drugs due to its inhibitory effect on P-gp activity. The first bioavailability booster to receive scientific validation was piperine. For instance, piperine inhibits cytochrome P450 3A4 (CYP3A4) and P-gp, both of which are involved in the first-pass clearance of numerous medications (Zhou 2008; De Almeida et al. 2020). About 50% of marketed drugs are metabolized by CYP3A4 alone (Bhardwaj et al. 2002; Zhou 2008). Piperine inhibits β-catenin nuclear translocation in the HCT116 colorectal cancer cell line, reduces proliferation and migration of other colorectal cancer cell lines HCT116, SW480, and DLD-1, and does not affect the migration rate of IEC-6. Piperine suppresses the binding of TCF/LEF to DNA, hinders the movement of β-catenin into the nucleus, and can directly bind to the promoter, thus restricting the expression of Wnt target genes (Sarkar et al. 2010). According to the molecular mechanism of piperine's interaction with DNA, which has been clarified by Haris and colleagues, piperine binds to a tiny groove in DNA (Haris et al. 2015). The key excretory organs, the kidney, and the liver, which in mammals check for detoxification, can both be impacted by cancer therapy. Nevertheless, histological examinations revealed that the primary organ impacted by 5-FU combined piperine therapy is the liver. Most chemotherapeutic drugs, such as 5-FU, inhibit the immune system since they have detrimental side effects and kill many normal cells in addition to tumor cells (Hou et al. 2015). The association with piplartine, but not piperine, prevented leukopenia observed with solitary 5-FU treatment, suggesting that piplartine has a protective effect against the delayed hematopoietic depression caused by 5-FU. No significant changes were observed in the biochemical, hematological, or histological parameters tested when 5-FU and piplartine were combined (Shaheer et al. 2020). Huo and colleagues, for example, discovered that piperine suppressed the proliferation of HT-29 cells in vitro in a dose-dependent way. A study by Shaheer et al. found that piperine pretreatment enhanced radiosensitivity in HT-29 cells by causing apoptosis through a mitochondria-dependent mechanism (Shaheer et al. 2020). The anti-CRC characteristics of piperine have been confirmed by this research. Different kinds of tumor cells are induced to undergo apoptosis by piper nigrum and its constituents. For example, it was shown that piperine nigrum ethanolic extract, enriched with piperamides, might inhibit the growth of Ehrlich ascites carcinoma by inducing cell cycle arrest and promoting programmed cell death.Piperine may accelerate the HT-29 cell's endoplasmic reticulum stress-induced programmed cell death (Wong 2011; De Souza Grinevicius et al. 2016; Gupta and Pathak 2020).

Combinatorial effect of piperine and curcumin

CUR is almost insoluble in water, but it is very stable at the acidic pH of the stomach. According to studies on animals, CUR has a low bioavailability and requires large doses to be effective since it is rapidly broken down, transformed into glucuronide in the intestinal mucosa, returned to the lumen,

and removed by feces. Since CUR glucuronides do not prevent inflammation or cell division, it is possible that their bioactivity could be increased by converting to CUR conjugates. It has been documented that piperine (PIP) controls intra-enterocyte glucuronidation, which raises the bioavailability of dietary phenols like CUR and some medications. It has been shown that adding PIP to formulations containing CUR raises the drug's intra-intestinal and plasma concentrations, which enhances its anti-inflammatory and anti-cancer effects (Wang et al. 1997; Shoba et al. 1998; Lambert et al. 2004). PIP and CUR have the potential to function independently or in combination to inhibit mTORC1 signaling in the intestinal epithelium, potentially leading to the formation of tumors and inflammatory conditions. PIP was found to be a less potent inhibitor of mTORC1 in HT-29 and Caco-2 cells than CUR, except in differentiated Caco-2 cells (Kaur et al. 2018). Since Cur is a substrate of P-gp, P-gp can pump Cur out of tumor cells, which would reduce the amount of drug that accumulates in tumor cells. Various methods are being investigated to improve Cur's bioavailability despite formulation problems, including liposomes, nanoparticles, phospholipid complexation, cyclodextrin complexation, and solid dispersions (Bisht et al. 2007). Pip inhibits drug metabolism in Caco-2 cells through CYP3A4 and P-gp-mediated efflux, enhancing P-gp's ATPase activity at low concentrations and decreasing it at high ones. By downregulating transporter gene expression, Pip successfully suppresses P-gp, MRP1, and breast cancer resistance protein, boosting the efficacy of chemotherapy and reversing MDR in both short- and long-term treatments (Bhardwaj et al. 2002; Kurien et al. 2007; Li et al. 2011). BioPerine® capsules are a commercial product that can be purchased with Pip (Sabinsa Corporation, East Windsor, NJ, USA). This chemical is still underutilized despite its safety and pharmacological activity since there isn't a good delivery method that can produce enough therapeutic levels in vivo (Tang et al. 2017). However, curcumin exhibits minimal bioavailability due to its poor water solubility (0.6 g/mL); its serum level is just 60 nM. In addition, a significant portion of curcumin is inactivated during the liver metabolic process. Its peak concentration can be seen 1–2 h after eating, and its concentration in plasma does not surpass 1 mol. Curcumin is a drug that has been the subject of numerous attempts to improve its solubility in water and bioavailability. This is because curcumin is safe to use, has low toxicity, and has a great deal of potential to promote health. It benefits the human body in a multitude of ways. Piperine is currently the most widely used solution in dietary supplements. Piperine reduces an organism's metabolism of curcumin and functions as a bioenhancer (Górnicka et al. 2023). Curcumin and piperine, as well as individual and combination phytochemicals that reduced TNF- and COX-2 levels, have shown anti-inflammatory properties in colon cancer—phase II clinical research using curcumin comprised patients at high risk of colorectal neoplasia. When 4 g of curcumin was given orally every day for 30 days, individuals with colorectal cancer experienced a significant reduction in aberrant crypt foci (Carroll et al. 2011). By blocking its metabolism, piperine drastically increases the bioavailability of curcumin by up to 2000% (Shoba et al. 1998).

Conclusion and future perspectives

This review has demonstrated that MDR represents the primary barrier to cancer treatment. The traditional one-drug, one-target hypothesis cannot overcome chemotherapy resistance due to its multifactorial nature. Additionally, these drugs are harmful to normal cells. Drug resistance is the main reason why cancer treatments rarely work, even with tremendous advancements in the development of novel chemotherapeutic agents. Drug resistance is caused by several events, including drug efflux, DNA repair, drug inactivation or target alteration, apoptotic disruption, and epigenetic modifications (Klopfleisch et al. 2016). The goal of numerous studies has been to create efficient resistance modulators that can defeat the MDR found in human malignancies. Clinical trials are being conducted to investigate potent MDR modulators. Herbal ingredients have been used for centuries without causing any negative side effects, which is why they are the subject of many current studies. tetrahydro curcumin, a significant human metabolite, prolongs MDR-reversing action and inhibits ABC drug transporter efflux activity (Limtrakul 2007). Because of its chemical structure and balance of hydroxyl and methoxy groups, curcumin I is the most effective inhibitor of the three-drug transporters, MXR, MDR1, and MRP1. This makes it more suited for binding to the drug-binding site (Kwon 2014). The World Health Organization and the Centre for Development Studies report that colorectal cancer ranked third globally after lung cancer, is expected to reach 24 million new cases by 2035 (Pilleron et al. 2019). 5-FU is the most common chemotherapeutic drug for its treatment. Clinical applications for 5-FU-based therapy have proven widespread in the treatment of many forms of cancer. However, significant toxicity and drug resistance restrict its therapeutic efficacy. This review paper explores the potential synergistic effects of piperine, curcumin, and 5-FU on colon cancer, aiming to improve sensitivity and reverse 5-FU resistance in response to colorectal cancer.

Although curcumin has demonstrated great effectiveness in treating cancer and has low toxicity and good safety, its primary drawbacks are limited solubility in water, poor stability, and poor bioavailability. To solve this issue, techniques such as using piperine in combination as an enhancer are applied. Thus, knowing curcumin's role and mechanism and the best approach for increasing its bioavailability, can

help us apply this potent natural ingredient to boost antitumor drug efficacy and counteract the impacts of drug resistance. By affecting important regulatory proteins, piperine keeps the balance between quiescent and proliferating cells. It enhances cell death by influencing ER stress and autophagy. As previously highlighted, it binds at NBD between the linker peptide and the consensus sequence of the walker ATP loop. By competing with the ATP binding site, piperine inhibits MDR-mediated efflux drug metabolism and lowers the activity of ATPase at high concentrations. When combined with curcumin, it can increase the uptake rate of curcumin by decreasing the rate of metabolic breakdown, exceeding the residence time, changing the dynamics of membrane lipids, and altering the confirmation of enzymes in the intestine by blocking curcumin efflux through MDR transporters. In addition, we suggested a combinatorial mixture of natural and synthetic chemotherapeutic medications for the treatment of colorectal cancer. This research proposal may be helpful in the advanced stages of cancer. We believe this notion could be used as a novel and affordable colorectal cancer therapy approach if it proves to be valid. It could potentially evolve into a tactical scheme for managing different malignancies.

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