

# Literature review: treatment design to overcome anticancer drug resistance

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**ABSTRACT:** One of the main causes of death in the world today is cancer. Chemotherapy is one treatment that cancer patients may utilize. Anticancer medication resistance, which might forecast a rise in treatment failure rates among cancer patients, poses a challenge to the current use of anticancer treatments. Numerous investigators have studied potential approaches to combat anti-cancer medication resistance. The purpose of this literature review is to provide information on treatment planning that can be applied to counteract anti-cancer medication resistance. Cancer is one of the leading causes of death in the modern world. One therapeutic option available to cancer patients is chemotherapy. The current usage of anticancer medicines is challenged by anticancer medication resistance, which may predict an increase in treatment failure rates among cancer patients. Many researchers have looked into possible strategies to fight drug resistance to anti-cancer medications. This review of the literature aims to give information on treatment planning that can be used to combat drug resistance to anti-cancer medications.

**KEYWORDS:** Anti-Cancer; Chemotherapy; Literature Studies; Resistance.

## INTRODUCTION

Millions of people have died from cancer in the 21st century, including those from the breast, brain, bladder, non-small-cell lung, prostate, kidney, colorectal, lymphoma (Non-Hodgkin), oral, and oropharyngeal, as well as skin (melanoma and non-melanoma) [1]. According to data from Globocan 2020, there were a total of 19.292.789 instances of cancer (all forms, regardless of gender or age), and there were 9.958.133 deaths (51%) as a result [2]. Several treatment approaches have been investigated to eradicate cancer, ranging from highly invasive surgical incisions to radiation abatement and various chemotherapy approaches [3]. Researchers and primary care physicians have made these decisions, and they are being used to significantly extend patients' lives with cancer. Although numerous therapeutic approaches have been created to combat cancer, it is difficult to quickly remove the tumor and increase the patient's survival [4].

Inactivity, alcohol usage, a low intake of fruits and vegetables, smoking (22% of cancer fatalities), and having a high body mass index are all factors that have been linked to an increased risk of developing cancer. About a third of cancer deaths are thought to be caused by these causes. Women are more likely to develop breast, cervical, lung, thyroid, and colorectal cancers than men, who are more likely to develop prostate, pulmonary, colon, liver, and stomach cancers [5]. Radiation therapy, surgery, immunotherapy, endocrine therapy, and gene therapy are a few of the various cancer treatments. The most typical cancer treatment is still chemotherapy [6].

Approximately 50% of all cancer cases show resistance to chemotherapy even before treatment begins (intrinsic resistance), while in the majority of cases, resistance develops during treatment (acquired resistance). Efforts to overcome chemotherapy resistance have so far been unsuccessful, due to the high heterogeneity and complexity of cancer cell biology, with wide individual variations. Although understanding of resistance mechanisms has improved in recent years and led to the development of new, more specific drugs, these drugs also face significant failure rates and toxicity. The addition of new anticancer drugs has not been able to effectively reduce the incidence of drug resistance to date [7]. Cancer drug resistance often occurs in patients with lung cancer, breast cancer, ovarian cancer, pancreatic cancer and others [8].

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The most difficult part of treating and preventing cancer is the rising resistance to currently existing medications, which accounts for more than 90% of chemotherapy failures. This resistance is similar to that seen in the treatment of infectious disorders [9]. It appears to be a significant obstacle and permits cancer to proliferate when chemotherapy drugs are present [10]. Repeated use of one type of anti-cancer agent typically results in significant resistance, which can then progress to the same or completely unrelated medications with comparable mechanisms of action. The term "multidrug resistance" (MDR) refers to this mechanism [9]. In this literature study, the researchers presented data related to treatment designs that could be used to address anti-cancer drug resistance. A literature review was conducted to determine the development of alternative treatments for patients who experience resistance to cancer drugs from research that has been conducted.

## ▪ MATERIALS AND METHODS

This research uses the Literature Review method, that is, by conducting searches and gathering the necessary information from various primary sources that are scientifically reliable. The data search on this study was done with the keyword "Overcoming for Multidrug Resistance in Cancer" through Google Scholar and Pubmed. Data that can be used as a sample in this study must meet the inclusion and exclusion criteria. The criteria for inclusion in this study that is articles that contain puzzles about how to deal with resistance to anti-cancer drugs, the scope of publication of articles in 2013-2023, and the articles collected should be in full-text form. Exclusion criteria for this study are articles that don't discuss how to deal with anti-cancer drug resistance and data or inaccessible articles.

## ▪ RESULTS

After collecting data through Google Scholar and Pubmed, 28 articles were obtained that could be used as a basis in the study of this literature. Each article discusses related designs that can be used to deal with resistance to anti-cancer drugs. In this study, we discussed five treatment designs that can be used to deal with resistance to anti-cancer drugs.

Chemotherapy resistance is a common cause of treatment failures in the recovery of cancer patients. Tumor resistance develops not only in response to a single cytotoxic agent but also in response to a wide variety of therapies that target various cellular structures and molecular targets. The term "multidrug resistance" (MDR) refers to this condition. The development of MDR led to the use of large dosages of medication to combat ineffectual resistance, the appearance of hazardous side effects, and growth in resistance. MDR is to blame for the decline in the overall efficacy of cancer chemotherapy and substantially restricts the effectiveness of chemotherapy in several prevalent cancers [11]. However, some designs can be done to deal with MDR.

## ▪ DISCUSSION

### **Change the chemotherapy regimen**

Chemotherapy's main goals are to stop the growth and shrinking of the tumor mass while preventing invasion and spread. However, single-drug-based therapy regimens are frequently vulnerable to tumor cell resistance. Modified therapy regimens have become one of the most popular options for dealing with the overwhelming. Typically combining two separate medications at a reduced dose [12]. Modified therapy regimens, for example, differ from combination therapies, which mix several forms of treatment, like radiation and surgery. Many medications generally have synergistic effects that significantly increase the efficacy of combination therapy regimens. Due to lower doses than those given alone, this lessens the negative effects of the medication. Alkylating agents, antimetabolites, cytidine analogs, folate antagonists, as well as purine and pyrimidine analogs, antimicrotubular agents, antibiotics (bleomycin, actinomycin D, and leptomycin), as well as others (hydroxyurea, tretinoin), are among the classes of medications that are more frequently used as supplemental therapies [13].

Through multi-target therapy, which uses medications that function through various mechanisms, such as cisplatin and etoposide for SCLC (Small Cell Lung Cancer), the risk that cells will develop drug resistance to a single drug is considerably decreased. Additionally, by significantly triggering the ablation of highly proliferative and metastatic cells, successive therapy regimens of several medications used in combination

limit the creation of resistant clones [14]. The establishment of standard therapy regimens in terms of medicine and dose is hampered by the fact that, despite the success of utilizing a combination of different drug classes, effectiveness frequently varies with the type of cancer. The stage of cancer that can respond to the medicine and spread to other places of the body also affects how well the adjusted therapy regimen works. Before choosing a modified therapeutic regimen, a number of additional parameters, including age, health issues, pharmacokinetics (solubility), and profiles, should be taken into account. The most common symptoms, such as nausea, vertigo, exhaustion, and loss of appetite, are unavoidable, despite the fact that toxicity is greatly decreased by the application of modified therapeutic regimens. P-gp inhibitor medication can be used to alter chemotherapy regimen designs [15].

P-gp inhibitors have been identified using a number of research, including cytometry testing, growth inhibition tests, transport tests employing Caco-2 monolayer cells, immunohistochemistry killing, and Western blotting techniques [16]. Caco-2 cell monolayers, derived from human colon adenocarcinoma, are a commonly used *in vitro* model for studying the intestinal barrier. These cells express most of the key intestinal transporters and enzymes, including those involved in the metabolism of methionine (Met) precursors. Therefore, the Caco-2 model is valuable for research on drug absorption, nutrient transport, and intestinal enzyme activity. The ATPase test is frequently employed to assess ATP levels and establish a connection between ATP consumption and the P-gp action's competitive mechanism. The thiol-reactive probe and Sistine scanning mutagenesis can be used to determine the residues that make up the drug-binding bags [17].

First-generation inhibitors are typically considered medicines with side effects that specifically target P-gp inhibition and are being explored for use in clinics [18]. Chemosensitizers function specifically to compete with chemotherapy since the import of the P-gp substrate inhibits it. There have been several attempts to create second-generation inhibitors of various medications, including dexverapamil and dexniguldipine. For instance, dexverapamil is the R-enantiomer of verapamil, and this second-generation inhibitor was explicitly created from the first generation of chiral medicines using an acetate combination. Through combinatorial chemistry and Quantitative Structure-Activity Relationship (QSAR), this third-generation modulator inhibits P-gp. It enables the development of molecules with favorable charge-specific properties at neutral pH and increased lipophilicity because of aromatic rings. Examples of the most popular third-generation modulators are tariquidar, zosuquidar, and elacridar [17].

### Mdr-related gene targeting

Research interest in controlling cancer factors or pathways by targeting MDR-related genes using particular gene deletion techniques or mRNA inhibition and alternative connections of the genes involved has been sparked by failures in the activity of different inhibitors. For instance, some studies demonstrate that blocking NF- $\kappa$ B members (RelA, c-Rel, and NF-B1) significantly lowers MDR in cancer via interacting with the consensus of the *mdr1* gene. Similar to the mutant IB-I inhibitor, *mdr1* messenger RNA (mRNA) and condensed ABCB1 expression in HCT15 cancer cells are caused by the NF- $\kappa$ B transcription factor. In a different instance, the protein OCT4-PG1 will prevent the interaction with the transcription factor OCT-4, which reduces the regulation of ABCB1 and alters the phenotype of MDR on the leukaemia cell line. Pre-mRNA alternative splicing is a crucial strategy for controlling ABC protein modulation and MDR expression levels in addition to direct inhibition [15]. Non-coding RNAs (ncRNAs), a short RNA subclass, control target proteins' expression, including those involved in cancer. Although some studies suggest that ncRNAs can be linked to cancer resistance and cell proliferation, some of them are employed as biomarkers to investigate treatment resistance in cancer. For instance, PCAT-1 knockdown reduces 5-FU resistance in colon cancer, which is associated with ncRNA transcripts related to prostate cancer lncRNA 1 (PCAT-1) [19].

### Natural product uses

Traditional Chinese Medicine (TCM), which frequently includes the use of natural items in addition to acupuncture, moxibustion, and physical therapy, has been used by the Chinese for treating illnesses for a very long time. Researchers may become interested in studying the use of natural products to combat cancer cells' medication resistance as a result of this. Wang et al. (2015) [21] used doxorubicin with or without osthole (osthol) to treat T24/ADM cells of bladder cancer. According to research, the IC<sub>50</sub> of osthole is 76.5 M, and at concentrations of 17 M or below, it is not harmful to cells. However, it was able to reduce the doxorubicin IC<sub>50</sub> from 1.0 to 0.4 M at a concentration of 17 M, leading to a 2.5-fold rise in drug sensitivity. At doses of 5 g/mL or below, evodiamine compounds are not harmful to resistant and sensitive cells (A549Cisplatin's IC<sub>50</sub> was reduced at 0.25 g/mL from 76.7 to 6.7 g/ml, increasing the drug sensitivity of A549/DDP cells by 11.4 times. Mechanistic investigation revealed that evodiamine could decrease pIKK levels as well as MDR1 and Bcl-2

mRNA levels, indicating that the drug could function in a variety of ways to overcome drug resistance. Additionally, Celastrol exhibits notable anti-drug resistance activity. It can significantly raise the intracellular drug concentration, lower the amount of the MDR1 protein, and boost cell susceptibility to chemotherapeutics in K562/A02 cells by 117.9 times. In a hybrid experiment, it was discovered that embelin increased the susceptibility of drug-resistant K562 cells to the torubicin leaf by 7.5 times [21].

Evodiamine, peiminine, isorhynchophylline, berberine, ephedrine, ginsenoside Rb1, oridonin, oxymatrine, methyletherscutellarein, sodium norcantharidate, phenylpropanoid glycoside, retinoic acid, schizandrin A, and baicalin are among the 14 single compounds that have been shown for the first time to be able to combat cancer [21].

### Nanomedical design

Given that chemotherapeutic drug resistance is associated with efflux proteins that are found mainly in nuclear membranes and blood but not in mitochondria [22]. One of the novel approaches to combating drug resistance to chemotherapy is using chemotherapeutic drugs that can enter mitochondria. [23]. To promote tumour accumulation, cellular absorption, mitochondrial targeting, intracellular localization, and addressing MCF-7/ADR breast cancer drug resistance, Yu et al. (2019) used a "shell-core" nanosystem (DOX-PLGA/CPT/PD) based on weak acid, charge-reversible, triphenylphosphonium (TPP). PLGA and C18-PEG2000-TPP (CPT) are used to create positive-charge mitochondrial targeting lipid-polymer hybrid nanoparticles (PLGA/CPT) [25].

Hypoxia-induced factor-1 (HIF-1) can be activated and stabilized when chemotherapeutic medicines are given to tumour cells [26]. HIF-1 controls the multidrug resistance protein (MRP), P-glycoprotein (Pgp), and Bcl-2, which all contribute to drug resistance [27]. HIF-1 can also control glutathione levels, which can bind to heavy metal ions like cisplatin [28]. Thus, blocking the HIF-1 pathway while receiving chemotherapy may be a viable strategy to prevent the development of chemotherapeutic resistance [29]. Acriflavine has been demonstrated to bind to HIF-1 and can significantly inhibit HIF-1, which can be a valuable tactic for chemotherapy sensitization [30]. Research A novel micro-silica-based co-delivery method (PMONA) was created by Zhang et al. (2020) to counteract cisplatin-induced resistance. In the mesoporous silica nanoparticles of the polymeric mPEG-silane that are operated by the microemulsion technique, cisplatin is loaded to the nucleus [32]. Organosilica bridges with tetrasulfide linkages are combined to produce nanoparticles that release medicines when tumour-specific glutathione is present. Electrostatic interaction loads acriflavine into the micropore region, resulting in nanoparticles with a diameter of 45 nm that are charged with acriflavine. The organosilica shell outside of PMONA can be broken down by intracellular glutathione after internalization by cancer cells, leading to nanoparticle breakdown, drug release, and synergistic modulation of several cancer-related signalling pathways. In a ten mM glutathione-containing media as opposed to a 10 M glutamate-containing medium, cisplatin and acriflavine release at a faster and greater cumulative rate. Organ PMONA osilics' tetrasulfide linkages enable the breakdown and release of a medication that reacts with glutathione. demonstrated greater cell cytotoxicity after being incubated with A459 cells, causing more apoptosis than single drug-laden nanoparticles via inhibiting HIF-1-related proteins and decreasing intracellular glutathione levels.

### Tumour suppressant genetic function recovery design

The molecular mechanisms underlying anticancer drug resistance are diverse and complex. They include increased expression of Multi-Drug Resistance (MDR) efflux pumps of the ATP-binding cassette transporter superfamily, reduced drug intake, quantitative and qualitative changes in intracellular drug targets, drug sequestration in intracellular and intercellular compartments, induction of anti-apoptotic mechanisms, activation of signalling cascades, and modifications to the microenvironment. According to specific research, deleting tumour suppressor genes (TSGs) also contributes to chemoresistance [33]. The pathological process of cancer formation involves the interaction of oncogenes and tumour suppressor genes. It has been demonstrated that the effects of genomic integrity, cell cycles, and cell proliferation can cause TSG to release its anticancer activity [34].

TSG inactivation has a substantial impact on the basic processes involved in cancer, such as cell division, DNA repair, and cell proliferation. In order to combat cancer medication resistance, the TSG targeting method can offer choices for cancer care. The mechanisms causing the loss of the TSG function include epigenetic regulation, transcriptional regulation, phosphorylation regulation, ubiquitin-proteasome regulation, and TSG intracellular translocation. To overcome drug resistance, TSG functional restoration uses tiny molecule drugs



that target these non-genetic processes. Some substances, particularly in the fight against cancer treatment resistance, have anti-tumour characteristics, including Nutlin-3, 5-azacytidine, DW22, and Selinexor [35].

Some of these epigenetic agents have received FDA approval and demonstrated efficacy in treating clinical cancer. The epigenetic agent is a promising anticancer treatment because of its excellent selectivity, minimal toxicity, and effective anti-tumour activity [36]. In clinical trials, some epigenetic agents, including HDACi vorinostat and DNMTi 5-azacytidine, had synergistic effects with additional anticancer medications, demonstrating that they function as an agent of sensitivity to anticancer therapy. Researchers were interested in epigenetic regulation's function in cancer because it would reveal fresh knowledge about how to target TSGs and combat medication resistance. Drug resistance is tightly associated with m6A RNA modification. The FOXO3 mRNA stabilization mediated by m6A is associated with the loss of sorafenib-induced METTL3 resistance in HCC. Thus, a new pharmacological weapon against drug resistance may be provided by the novel chemical that targets the m6A modulator [37].

Based on the discussion above, researchers assume that one alternative to overcome cancer drug resistance is the utilization of natural materials. This is because the utilization of natural materials is easy to obtain and does not require large costs.

## CONCLUSION

Resistance to anticancer drugs is a new challenge nowadays, which increases the interest of researchers in conducting research related to strategies that can be used to tackle anticancer resistance drugs. Based on the results of this literature study, there are five designs or strategies that can be used to deal with resistance to anticancer drugs, including changing chemotherapy regimes, targeting MDR-related genes, the use of natural products, nanomedicine and restoring the function of tumour suppressant genes.

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