# How cancer drugs are discovered and developed

**Dr.G.Ariharasivakumar[1], G.M. Mathiazhagan[2] , K.Monica[3] , E . Santhosh kumar[4] , R.Vinoth kumar[5]**

Professor & Head
Department of pharmacology, KMCH College of pharmacy, Coimbatore.

**Abstract: Cancer may be a complex malady and its genesis and progression are extraordinarily complex.The largest downside within the malignant neoplasm drug development is deed of multi drug resistance and relapse. Classical chemo therapeutics directly target the polymer of the cell, whereas the modern anticancer medication involve molecular-targeted medical care reminiscent of targeting the proteins possessing abnormal expression within the cancer cells.Standard ways for the complete demolition of the cancer cells tested ineffective.Targeted therapy was successful in bound malignancies however, the effectiveness has usually been restricted by drug resistance and side effects on traditional tissues and cells.Since previous few years, several promising drug targets are known for the effective treatment of cancer. This review article describes a number of these promising malignant neoplasm targets that embrace kinases, tubulin, cancer stem cells, being antibodies and microtuble targeting agents. In addition, promising drug candidates underneath varied phases of clinical trials also are described. Multi-acting medication that simultaneously target completely different neoplastic cell signal pathways might facilitate the method of effective anti-cancer drug development.**

**Keyword: Anticancer, Various target statergies, Tubulin, Kinases, Cancer stem cell, Monoclonal antibodies**.

## 1. INTRODUCTION

Uncontrolled cell development results in cancer, which is a leading cause of mortality globally. It affects more than 60 different human body organs and has more than 200 different forms of cases. Most cancers are difficult to recognise at the initial level, and tumour spread can cause cancer-related mortality in later stages [1–3].Surgery, chemotherapy, and radiation therapy are some of the several approaches used to treat cancer. These can be used separately or in combination. Traditional cancer treatments directly affect the DNA of the cell, but modern anticancer medications use molecularly focused therapy, such as focusing on proteins that have aberrant expression in cancer cells. Compared to conventional anticancer treatments, these molecularly targeted therapies selectively destroy cancer cells while being less hazardous to normal cells [4].Certain cell signalling pathways that support the malignant phenotype of cancer cells are inhibited by targeted medicines. Chemotherapy has steadily become better thanks to the creation of brand-new anticancer medications. Targeted chemotherapy has been effective in treating some cancers, but it has serious drawbacks, including the development of drug resistance and damage to healthy tissues and cells.Many cancer cells overexpress drug transporters, which lowers intracellular medication concentrations. Moreover, increased medication resistance may be brought on through the development of point mutations.A significant barrier to the efficient treatment and total elimination of cancer is multidrug resistance (MDR).To treat cancer, several drug targets have been found. The majority of molecularly targeted drugs were useless because of toxicity or effectiveness issues. Researchers are being challenged to concentrate on the pharmacological targets that can aid in the total eradication of the illness by recent work in the field of molecular biology and a better knowledge of the molecular pathology of cancer [5]. It has been noted that identifying or validating kinase inhibitors accounts for around 30% of anticancer drug research efforts. In addition, monoclonal antibodies and multi-targeting anticancer treatments have drawn the attention of researchers for producing effective medications for the complete eradication of illness. Clinical studies for a variety of possible medication candidates are at various levels.In this review article let us discuss each of the cancer targets in detail.

## 2. KINASES

To treat cancer, several drug targets have been found. The majority of molecularly targeted drugs were useless because of toxicity or effectiveness issues. Researchers are being challenged to concentrate on the pharmacological targets that can aid in the total eradication of the illness by recent work in the field of molecular biology and a better knowledge of the molecular pathology of cancer. It has been noted that identifying or validating kinase inhibitors accounts for around 30% of anticancer drug research efforts. In addition, monoclonal antibodies and multi-targeting \santicancer treatments have drawn the attention of researchers for producing effective medications for the complete eradication of illness. Clinical studies for a variety of possible medication candidates are at various levels [6,7].Protein kinases control the majority of cellular activities and are involved in the majority of signal transductions in cells. They reversibly phosphorylate proteins after translation. They are engaged in a variety of cellular processes essential for cell survival, including differentiation, cell proliferation, apoptosis, and metabolism of diverse substrates. The hydroxyl group of serine, threonine, and tyrosine is transferred one phosphoryl group from the ATP's - position by protein kinases, which are ATP-dependent phosphotransferases.The Mg2+ ion often catalyses the reaction and aids in ATP binding [8-10].While the protein kinases' amino acid sequences differ significantly, most of them have comparable 3D protein structures [11]. The following is a description of some significant kinases and their function in the creation of anticancer drugs:

### 2.1. Tyrosine kinases

Tyrosine kinases (TKs) are enzymes that are essential for controlling the growth and survival of cancer cells.Tyrosine residues in polypeptides get phosphate through the action of TKs. There are around 30 distinct families of tyrosine kinases, including EGFR, VEGFR, and NGF. Tyrosine kinases, which may be categorised into receptor tyrosine kinases and non-receptor

tyrosine kinases, are 90 tyrosine kinases and 43 tyrosine kinase-like genes found in the human genome [12,13]. A receptor tyrosine kinase is made up of a transmembrane domain, an intracellular tyrosine kinase domain, and an N-terminal extracellular ligand- binding domain (LBD). Three subregions—the adenine region, the phosphatebinding area, and the sugar region—can be further subdivided into the ATP-binding site of tyrosine kinases [14].Activation of tyrosine kinases leads to activation of variety of signalling pathways. A protein that has a Src homology 2 (SH2) domain phosphorylates a TK receptor when it binds to it. A variety of kinases are further phosphorylated by the activation of this effector protein. The p42/44 MAPK pathway is triggered by protein kinase C's (PKC) phosphorylation of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK). Different transcription factors are activated by phosphorylated MAPK, which also controls cell proliferation [14, 15].Other tyrosine kinase-activated pathways, including as PI3K, Raf, Ras, p38 MAPK, and FAK, are also in charge of cell migration and reconfiguration, which in turn leads to tumour metastasis. Tyrosine kinases are being investigated as a key target for the development of anticancer drugs due to their well-established function in many malignancies.

### 2.2. Cyclic dependent kinase

The heterodimeric proteins known as cyclin-dependent kinases (Cdks) are made up of a catalytic Cdk subunit and a regulatory cyclin component. Cdks are essential for the advancement of the cell cycle, cellular transcription, and apoptotic pathways. Twelve different kinds of Cdks exist in the mammalian genome, and five of them—Cdk1, Cdk2, Cdk3, Cdk4, and Cdk6—are directly responsible for regulating the cell cycle. The other CDKs are engaged in the interphase of the cell cycle, whereas CDK1 has a function in the mitotic phase [16].The main obstacle to developing reversible Cdk1 inhibitors is the lack of particular molecular tools, even though Cdk1 is a key target for cell cycle arrest in tumour cells. It is thought that a long-term blockage of Cdk1 might have a number of harmful consequences on healthy cells. Cancers of various sorts often have mutant Cdk/cyclin complex subunits. In leukaemia, lymphoma, neoplasia, colorectal, esophageal squamous cell, head/neck, lung, kidney, breast, and prostate cancers, for instance, cyclin D1 is shown to be overexpressed.During typical mitosis, the Cdk1/cyclinB complex transiently and poorly phosphorylates the Bcl-xL and Bcl-2 proteins, but in cancer situations, these proteins were shown to be significantly phosphorylated [17]. Cdks therefore became a desirable group of targets for the development of anti-cancer drugs. As possible anti-cancer treatments, several compounds that block cell cycle kinases have been created and are now being studied in clinical settings.

### 2.3. Kinases inhibitors

Imatinib, a small-molecule inhibitor, was initially used to target BCR-AbL in the treatment of chronic myeloid leukaemia (CML). As a result, several imatinib derivatives have been created and tested in an effort to create the next generation of kinase inhibitors and learn more about how they work. The US Food and Drug Administration has approved 30 small molecular inhibitors and seven therapeutic antibody kinase inhibitors to date for the treatment of various malignancies.In the past three years, more than half of these have been granted [18,19].

**Table 1.Recently approved protein kinase inhibitors**

| | |
|---|---|
| 1. Imatinib | 2. Gefitinib |
| 3. Ibrutinib | 4. Bimetanib |
| 5. Palbocicnib | 6. Osimertinib |
| 7. Lenvatinib | 8. Alectinib |

Due of its ability to target several kinases, imatinib is the most effective kinase inhibitor. After receiving clearance for the therapy of chronic myelogenous leukemia, it was also given the go-ahead for the treatment of a number of other malignancies, including gastrointestinal stromal tumors (GIST) (targeting KIT and PDGFR) [20], recurrent and/or metastatic fibrosarcoma protuberans (targeting PDGFR), hypereosinophilic syndrome (targeting PDGFR) [37].The bulk of the kinases still need to be investigated, and just a tiny subset of them are being targeted for the creation of anti-cancer drugs [21]. Understanding the kinase enzymes' "switch on" and "switch off" mechanisms can aid in the creation of protein kinase inhibitors that have the potential to become effective therapeutic candidates for the total eradication of cancer.

## 3. TUBULIN OR MICROTUBULE

Compared to normal cells, cancer cells proliferate and develop rapidly. The microtubule is one of the essential elements needed for cell division and cell proliferation, hence microtubules-targeting compounds are being investigated for the development of anti-cancer drugs [22,23]. Microtubules are cytoskeletal elements that are found throughout all cells and are created when a tubulin heterodimer and bind together. These are crucial for the formation and maintenance of cell shape, as well as for cell division, reproduction, signaling, and motility [24].Tubulin heterodimers and microtubules coexist in a dynamic balance. Both the monomer units (α and β)of tubulin includes a GTP molecule which binds at the dimer interface of the α -subunit in an irreversible fashionand is non-hydrolysable whereas, GTP molecule of heβ-subunit of tubulin bounds in a reversible way and is exchangeable with GDP molecule. The,-tubulin heterodimer functions as a monomer unit, and the production of protofilaments is caused by the head-to-tail attachment of one tubulin monomer's -polypeptide to another monomer's -polypeptide. A cylindrical microtubule wall is created by the parallel arrangement of thirteen protofilaments.The -subunit of tubulin should be GTP-bound during the microtubule polymerization cycle. The bulk of the beta-tubulin in the microtubule transforms to GDP-bound form after adhering to the microtubule, and the GTP of the beta-subunit irreversibly hydrolyzes to GDP. The positive end of the microtubule is covered by GTP-bound -tubulin. The GTP of the capped -tubulin is hydrolyzed to GDP for

the subsequent cycle of tubulin addition, and the exposed GDP -tubulin causes conformational changes that start the fast depolymerization of the microtubule with the release of the GDP- tubulin unit [25]. The development and shrinking of microtubules is primarily governed by stochastic phases that result from the polymerization and depolymerization of tubulin dimers. Dynamic instability is the term used to describe this pattern of non-equilibrium behavior [26].The therapeutic potential of tubulin has been evaluated by several research groups and the three-dimensional structure of the,-tubulin heterodimer has been thoroughly investigated [27]. Four distinct binding sites—taxane/epothilone, laulimalide, vinca alkaloid, and colchicine binding sites—allow a variety of small compounds with various structural characteristics to bind to tubulin. By stabilizing or destabilizing the polymerized state, microtubule binding agents engage with these locations on tubulin and alter microtubule dynamics. The microtubule, which is made of polymerized tubulin, contains the taxoid binding site, and ligands like paclitaxel help to keep the microtubule stable. Comparably, laulimalide, which binds to a different location on the microtubules, can similarly encourage the polymerization of tubulin [28].The,-tubulin's three-dimensional structure Microtubule dynamics are essential for the correct attachment and movement of chromosomes during cell division [29]. An inhibitor's disruption of the microtubule dynamics of a cell prevents mitosis, which results in cell death. Consequently, altering microtubule dynamics is a key target for the creation of anti-cancer medications.

### 3.1. Microtubule stabalizing agents & their mechanism of action.

Microtubule stabilizing agents attach to tubulin in polymeric microtubule form and stop it from depolymerizing. Even when tubulin is in the GDP-bound form, these substances encourage the attachment of tubulin monomer units to microtubules.One of the two binding sites that enhance microtubule stabilization and halt depolymerization is engaged by microtubule stabilizing drugs. This results in cell arrest at the G2/M phase and disruption of spindle dynamics during cell division [30].The interactions at three areas of the tubulin, H3, S3, and M-loop, are significantly influenced by the ligands binding to the taxoid site. The M-loop of the -subunit interacts more with the H1-S2 and H2-S3 loops of the adjacent protofilaments when a taxoid binding ligand is bound, stabilizing the microtubule [31].Additionally, paclitaxel causes the M-loop to descend, enhancing interactions with the loops in the next monomer unit. The microtubule is unstable and depolymerizes as a result of GTP being converted to GDP in the tubulin - subunit. However, the interaction of paclitaxel results in certain structural alterations at the nucleotide binding site that counteract the hydrolysis of GTP. In contrast to the taxoid binding site, microtubule stabilizing drugs also bind to the LAU/PEL binding site [32].

### 3.2. Microtubule destabilizing agents & their mechanism of action

Chemical substances that bind to the vinca and colchicine domains disrupt microtubules and hinder tubulin polymerization. The bulk of interactions are limited to the - tubulin monomer and the colchicine binding site is situated at the interface between and -tubulin [33]. Colchicine joins with tubulin to create a complex, which it then adds to the microtubule, where it causes several conformational changes.These structural modifications render the microtubule polymerization process energetically unfavorable and stop it by sterically preventing further tubulin dimer addition at the ends [34]. The vinca binding pocket is located at the GTP-exchangeable site of the -subunit and is found on the longitudinal interface between two tubulin heterodimers. Numerous substances bind to the vinca domain, including vinblastine (VBL), vincristine (VCR), vindesine (VDS), and vinorelbine (VRL) [35].One of the key objectives for the creation of anti- cancer medications is tubulin. To find and create safer and more effective therapeutic candidates, a variety of tubulin targeting compounds have been synthesized and structure-activity relationship investigations have been carried out [36,37]. It is well known that changes in the expression of -tubulin isotypes and/or mutations in tubulin genes can result in drug resistance.P-glycoprotein-mediated multidrug resistance is the most prevalent mechanism for resistance to tubulin binding drugs [38]. Numerous studies have linked the III-tubulin isotype, which reduces the microtubule's stability and counteracts paclitaxel's effects, to paclitaxel resistance [39].Therefore, it is necessary to chemically modify the current drug molecules to reduce their affinity for the transporting proteins that cause multi-drug resistance. For the creation of efficient and secure anti-cancer treatments, several formulations of previously existing tubulin binding drugs, such as paclitaxel, are now being studied in clinical settings.

## 4. CANCER CELL

The term "cancer stem cell" (CSC) refers to a kind of tumour cell that has the ability to self-renew, differentiate, and proliferate indefinitely. Asymmetric division and self-replication allow the CSC to maintain their proliferative capacity. Over a brief amount of time, CSCs can create daughter cells that can multiply extremely quickly. These cells can differentiate and form the majority of non-CSC cells in the tumour mass. CSCs are in charge of the development of tumours and the upkeep of a population of rapidly growing cells within them [40, 41].The first CSCs identified in human acute myeloid leukaemia (AML) were leukemic stem cells (LSCs) [42]. In the breast cancer cell investigation, it was shown that a very tiny fraction of self-renewing breast tumour cells with rudimentary surface immunophenotype and differentiation capacity yet retain a new tumour starting capability [43]. In several tumour types, including the brain, prostat, melanoma, colon, lung, ovarian, and chronic myelogenous leukaemia, the CSCs have now been found and described. Therefore, it is thought that distinct cancer types contain a subset of tumour cells that resemble stem cells, and that the stem-like fraction substantially or entirely possesses the ability to initiate and advance tumours.The population of CSCs must be targeted for the development of anti-cancer drugs. CSCs are essential for the development and spread of tumours because they have the capacity for long-term proliferation. The CSC population must be entirely eliminated in order to halt the spread of the illness. It is, therefore, incredibly challenging to target the CSCs population. Similar to normal tissue stem cells, CSCs may have a variety of distinguishing qualities that render them resistant to a variety of anti-cancer treatments.These cells have a reduced rate of proliferative growth, enhanced DNA damage repair, increased production of anti-apoptotic proteins, and transporters for multiple drug resistance [44].The majority of CSC-targeting treatments involve blocking cell signalling pathways, which are essential for the survival and operation of the CSC population. By focusing on the CSC niche, it may be possible to indirectly inhibit a number of CSC functions and get around many of the elements of intrinsic drug resistance associated with CSCs. The effects of traditional cytotoxic radiation or chemotherapy on CSCs may be

increased by disrupting the supporting vascular niche, and the effects of other CSC-targeted treatments may also be amplified.

### 4.1. Notch pathway

In several animals, notch receptors play a crucial role in regulating the cell destiny of distinct ancestries.Mammals typically have four Notch members, and each of them has an extracellular region with several repetitions of the epidermal growth factor [45]. When transmembrane ligands from one cell connect to the Notch receptor found on a neighbouring cell, the Notch signalling pathway is activated. It results in the release of the Notch intracellular domain's (NICD) - secretase-mediated proteolytic [46].Then, NICD enters the nucleus where it interacts with the cofactor CBF1 to activate the target genes HES and HEY. The Notch's extracellular region interacts with its ligand to provide cell signalling that either prevents stem or progenitor cell development or promotes differentiation into certain lineages. Many malignant tissues, including as the breast, cervix, kidney, pancreatic carcinoma, leukaemia, neuroblastoma, myeloma, and medulloblastoma, have been discovered to overexpress notch ligands and receptors.Increased Notch activity has been seen in most tumour types, which encourages tumour development. As a result, inhibiting Notch signalling is a prospective therapeutic target for several malignancies.

### 4.2. Hedgehog Pathway

The hedgehog (Hh) family plays important role in development and differentiation of many tissues and its gene is divided into various groups[47]. pathyway gets activated when the protein bind to the receptor and it releases Smo and Gli1, Gli2 & Gli3 associated oncogene transcription proteins, which regulates cell proliferation and differentiation[48, 49]. It is also well known for the development of cancer resistant cells. Molecule which inhibit hedgehog pathway signalling results in overcome resistance[50, 51, 52].

### 4.3. Wnt Pathway

Cell survival and proliferation, as well as embryogenesis and cell development, depend on the Wnt signalling pathway. The canonical Wnt/-catenin signalling system mediates the self-renewal and maintenance of stem cells, including cancer stem cells.It is triggered by the binding of a Wnt ligand to cell membrane coreceptors and the activation of the target genes [53]. The Wnt gene family encodes 19 secreted glycoproteins with high cysteine content that bind to frizzled (Fzd) receptors [54]. The Wnt/-catenin pathway is disrupted by APC tumour suppressor or -catenin oncogenic mutations, which encourage the development of cancer stem cells in a range of malignancies.Drug-resistant leukemic stem cells were discovered to be targeted and eliminated in vitro and in vivo by the small molecule CBP/-catenin inhibitor ICG-001 [55]. Nonsteroidal anti-inflammatory medicines (NSAID) or vitamins that target E-cadherin (Vitamin A and Vitamin D) and cyclooxygenase 2 (Aspirin, a Wnt target enzyme) also function as inhibitorsof the Wnt signalling pathway.

### 4.4. NF-kB Pathway

In the cytoplasm of cells, structurally related proteins can form homo- or heterodimers to form nuclear factor-kappa B (NF-kB) [56]. In response to stimuli including viral and bacterial antigens, UV radiation, and cytokines (IL-2 and TNF-), it is a transcription factor that promotes the expression of target genes. Over 400 genes that are NF-kB targeted, including cytokines, chemokines, oncogenes, pro- and antiapoptotic proteins, growth factors, and cell adhesion molecules, have been discovered thus far [57,58].IkB is phosphorylated when IkB kinases are activated, and the proteasome breaks it free of the NF- kB dimer. The synthesis of particular proteins is then stimulated as a result of NF-kB dimer translocation to the nucleus and attachment to the kB binding pocket [59].In tumour cells, the NF-kB pathway's constitutive activity is what causes growth, angiogenesis, apoptosis resistance, and metastasis. Consequently, effective therapeutic drugs for the treatment of cancer may be created using inhibitors of the NF-kB pathway.

## 5. MONOCLONAL ANTIBODIES AND ANTI-CANCER THERAPIES

Immunoglobulins, another name for antibodies, are Y-shaped proteins that aid in the detection and expulsion of invading antigens like viruses and bacteria. In response to the presence of an antigen, the immune system produces these. Heterodimers made up of two light chains and two heavy chains make up antibodies. Disulfide bonds link each light chain to the long chain, whereas disulfide bridges link the heavy chains to one another [60]. In the late nineteenth century, the concept of employing monoclonal antibodies (mAb) to treat and diagnose cancer emerged. It is now among the most effective medicines for treating solid malignancies.Typically, antibodies recognise and mark foreign dangerous particles that are present in the body as the initial stage in the eradication of these foreign pathogens or abnormal cells in healthy persons. The targets that the antibodies have identified are then attacked and destroyed by different other immune system components of the body [61]. The sequence of amino acids present in the variable region determines the specificity of antibodies for a given antigen [62].Antibodies kill cancer cells in a variety of ways, including I direct antibody action, such as receptor blockade, inducing apoptosis, or delivering cytotoxic agents directly to target receptors; (ii) immune-mediated cancer cell death, such as regulation of T cell function and antibody-dependent cellular cytotoxicity (ADCC); and (iii) specific antibody effects on tumour vasculature[63].Despite some initial setbacks with monoclonal antibody therapeutics, the USFDA has recently authorised a number of monoclonal antibodies (mAbs) for clinical use.

**Table 2. Monoclonal antibodies and their targets.**

| MONOCLONAL ANTIBODIES | TARGETS |
|---|---|
| Rituximab | Non-Hodgkin's lymphoma |
| Trastuzumab | Breast cancer |
| Alemtuzumab | Chronic lymphocytic leukemia |

| | |
|---|---|
| Cetuximab PanitumumabBevacizumab | Colorectal cancer |

Tositumomab and ibritumomab are two radioisotope antibody conjugates that have been authorised for use in the treatment of cancer. Many mAbs are undergoing various stages of clinical trials for the treatment of various cancers because of the high success rate of this form of therapy.

## 6. VASCULAR TARGETING AGENTS

Given the tumor's accessibility to blood-borne medications, targeting the tumour vasculature is a successful cancer therapy method. The tumour cells multiply extremely quickly, necessitating a continuous flow of oxygen and nutrients. Hence, the formation of blood vascular networks is crucial for the genesis, progression, and metastasis of tumours. Vascular disruption agents (VDAs) have the ability to stop the blood supply to tumours [64,65]. VDAs target the established tumour vasculature, as opposed to anti-angiogenic drugs, which stop the development of new capillaries. Since they are poorly structured, convoluted, leaky, and made up of rapidly proliferating endothelial cells and an incomplete basement membrane, tumour vasculature are aberrant and distinct from those in healthy tissues.These variations provide a therapeutic window that VDAs may take advantage of to target the tumour vasculature specifically.

The majority of VDAs under development are microtubule-binding substances that function by causing endothelial cytoskeleton disruption, which increases vascular permeability and hastens channel closure [66].As a result, the toxicity of their side effects is rather low. Investigations into several substances, including combretastatins, that differ structurally are being done for VDAs [67].The production of cytokines such tumour necrosis factor-alpha is thought to be the mechanism of action of VDAs. VDAs are typically well tolerated and tumour selective, according to several clinical studies that have been conducted thus far. One of the issues with VDAs is that they frequently cause hypoxia and necrosis in the centre of the tumour, but unaffected tumour tissue at the periphery, leaving a viable rim of cells. These cells have good oxygenation and might be vulnerable to conventional cytotoxic substances.The first synthetic flavonoid to be identified as a vascular disruptor was FAA (flavones-8-acetic acid). In pre-clinical investigations, it showed strong anti-cancer efficacy despite being created as a non-steroidal anti-inflammatory drug.A potential vascular disrupting medication called combretastatin A-4P (CA-4P) (16) is now being studied in clinical settings in conjunction with other chemotherapy drugs. Using CA-4P as a single drug, three distinct phase I clinical studies have been finished [68]. Most of the patients' blood flow was found to have significantly decreased. Studies combining CA-4P with paclitaxel or carboplatin were also carried out. The combined therapy was found to be well tolerated, and the majority of patients responded favourably to the tumour in most cases [69].

## 7. MULTI DRUG RESISTANCE

One of the main drawbacks of the majority of chemotherapeutic drugs used to treat cancer is multi- drug resistance (MDR). In order to improve the efficacy of the anti-cancer treatment, newer molecular targets and chemotherapeutic drugs are continually being researched. Chemotherapy resistance might happen in two different ways [69].

Genetic changes present before to therapy cause the main or intrinsic resistance. The second form of resistance, known as secondary or acquired resistance, is brought on by the medication during therapy.Both forms of resistances are brought on by cancer cell genomic mutations and/or epigenetic modifications.Drug resistance can occur with targeted treatments such kinase inhibitors as well as with standard chemotherapy [70].A series of mutations in a specific group of genes that cause uncontrolled proliferation result in the formation of cancer cells [71]. Many mutations and complicated chromosomal rearrangements may be present in cancer cells. Moreover, different individuals may have various mutations in the same gene, which may cause a variety of cancers [72].Several times, it has been noted that different people \ssuffering with the same form of cancer may respond \sdifferently to the same medication regimen.A variety of mutations in the cancer cells, excess expression of the ATP-binding cassette (ABC) drug \transporters and improved DNA repair are some of the factors involved for the development of resistance to the chemotherapeutics [73]. Chemotherapeutic resistance can also occur through modifications in the drug pharmacokinetics and metabolism, modification of drug target expression or function, drug compartmentalization in cellular organelles and changes in the apoptotic signalling pathways such as mutant p53 [74].

Chemotherapy resistance is a significant barrier to the complete elimination and effective treatment of cancer. For the illness to be completely eradicated, a deeper knowledge of the molecular pathways behind medication resistance is necessary. One of the most promising areas of cancer research is the creation of new inhibitors for medication resistance pathway. Nevertheless, due to their high toxicity, the ligands created to target ABC transporters failed in clinical studies [75].

## 8. MULTI-TARGETING ANTI-CANCER AGENTS

The creation and development of medications intended to work against a specific target with high potency and selectivity is the only focus of anti-cancer drug discovery efforts.Targeting only one cell signalling route may not be effective due to the biochemical and genetic complexity of advanced-stage cancer [76].Certain medication combinations that can simultaneously target and disrupt disease-relevant signalling pathways are used in the latest anti-cancer therapy development tactics. The combination medications might have individual activity, different methods of action, separate toxicities, and non- overlapping mechanisms of resistance.In contrast to multi-targeting medications, combination treatment includes the simultaneous administration of two or more drugs, whereas combination therapy uses a single therapeutic molecule that can target numerous oncoproteins to accomplish the same result.

Drug discovery is paying more emphasis to designing and creating a single therapeutic molecule that can concurrently and specifically interact with many targets [77–79]. Drugs that target several targets are less likely to experience an upsurge in drug resistance mutations and may increase effectiveness in an additive or synergistic manner. Comparing a medicine's efficacy to that of a highly selective pharmacological agent, a drug that is active on several targets may be distinguished by an improvement. It is now well-established that simultaneously inhibiting many kinases is an effective therapeutic approach.Sunitinib, a potential

drug for the treatment of anaplastic thyroid cancer, was demonstrated to be able to suppress Akt and ERK1/2 phosphorylation and downregulate cyclin D1 in tests conducted in vitro and in vivo [80].The success of a single medication multi-target strategy will depend on a number of obstacles, the majority of which still need to be overcome. Multi-target compound rational design is still in its infancy and requires methodological development and broader application. Significant areas of interest include medication repositioning in various therapeutic domains, off-target toxicity prediction, and rational design of multi- target medicines.

## CONCLUSION

As cancer is a complex disease, a single target strategy has thus far failed to completely eradicate it. Cancer cells create a variety of intricate defence mechanisms to counteract the cytotoxicity caused by the medicine. Drug combinations that target multiple signalling pathways may prevent secondary resistance and boost therapeutic efficacy.Certain cancer cell lines responded well to the multi-targeting anti-cancer drugs, which partially alleviated the MDR problem. Chemo resistance is thus a substantial barrier to effective cancer treatment. The effectiveness of chemotherapy depends on our ability to better understand the mechanisms of resistance. According to this, emerging medicines against CSC are promising since they may destroy the CSCs while avoiding or reducing the toxicity of normal tissue stem cells. Combining traditional anti-cancer medications with CSCs-targeting therapies may be a potential approach to the management and total eradication of many tumours.

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