A-Review on Anticancer Agents: Conventional Drugs and Novel Target Specific Inhibitors

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ABSTRACT

The second-most common reason for death globally and a significant issue for human health is cancer. The focus of the current review is to discuss cancer treatment and issues with anti-cancer medications. Nearly all cell types can develop cancer, a very varied group of approximately 200 illnesses with at least one factor in common “uncontrolled cellular development” that results in aberrant cell proliferation. In solid tumors, cancerous cells may remain localized or in situ at the location of the initial lesion, or they may become locally progressed or metastatic to distant site. Ninety percent of all cancer-related fatalities are due to by metastasis. It is the primary determinant of whether malignancy is high-risk, requiring aggressive treatment, or low-risk, curable by active surveillance, surgical removal, or adjuvant therapy. Recent advancements in computational drug discovery methodologies have not only produced important insights into the field of cancer therapy but have also had a significant and impact on the development of novel anticancer medications. Within the scope of this review, we investigated potential therapeutic targets for anti-cancer drugs.

Keywords: Cancer, Anti-cancer agents, MAPK Inhibitors, PLK1 Inhibitors, HIF inhibitors, Aromatase Inhibitors.

INTRODUCTION

Cancer belongs to a group of serious diseases characterized by an abnormal and uncontrolled growth of cells or cell division. A clump of cells that behaves abnormally is called a tumour. It arises either when cells reproduce at a faster rate than they should or when they fail to die off at the appropriate time. Malignant tumours are those that are cancerous, while benign tumours are those that are not cancerous. The edges of a benign tumour are clean and uniform. Malignant tumours grow more rapidly than benign ones and have more erratic borders. Cancer cells can spread to other places of the body, where they might develop and create new tumours. This is referred to as metastasis. It occurs
when cells enter the circulation or lymph vessels. Every year, approximately 12,00,000 new cancer cases are reported in India. According to the most recent National Cancer Registry data (2022), one in every eight males and one in every nine women in India may develop cancer. Numerous variables affect the occurrence and forms of cancer, including age, gender, race, local environmental conditions, food, and genetics. In males, lung cancer is the most prevalent, followed by oral cavity and throat cancers, whereas cervical and breast cancers are the most common in females in India.

**Types of cancer**

Cancers are usually named for the organs or tissues in which they first arise. The type of cell that generated cancer, such as an epithelial cell or a squamous cell, can also be used to characterise it. There are about 200 different forms of cancer, however the majority fall into the following categories:

- **Carcinoma**
  The most typical type of cancer is carcinoma. They are made up of epithelial cells that line the body’s inner and outer surfaces.

- **Sarcoma**
  Sarcoma are cancers that begin in the bone and soft tissues, such as muscle, fat, blood vessels, lymphatics, and fibrous tissue (tendons and ligaments).

- **Leukaemia**
  Leukaemia is a type of cancer that start in the bone marrows in this type of cancer solid tumours are not formed. In Leukaemia, vast numbers of abnormal white blood cells (leukaemia cells and leukemic blast cells) build in the blood and bone marrow and crowd out normal blood cells.

- **Lymphoma**
  Lymphoma is a cancer that start in lymphocytes. These white blood cells, considered to be part of the immune system, combat illness. Lymphoma is defined by the accumulation of abnormal cells in the body’s lymph nodes, lymph arteries, and other organs.

- **Multiple myeloma**
  Multiple myeloma is a cancer that grows in plasma cells, that are a type of immune cell. Myeloma tumour cells are a type of plasma cell that is aberrant. They accumulate in the bone marrow and form tumours in bones throughout the body.

- **Melanoma**
  Melanoma is an example of cancer that arises from cells which differentiate into specialized melanocytes that produce melanin. Melanomas are most commonly found in the skin, although they can also develop in other pigmented tissues such as the eye.

- **Brain and spinal cord tumors**
  The tumors of the brain and spinal cord may appear in a number of ways. Tumors like this are named after the cell type that gave rise to them as well as the place in the central nervous system where they originally emerged.

- **Other types of Cancer**
  **Germ cell tumors**
  Germ cell tumor are types of tumors that start in the cells that make sperm or eggs. These tumors, whether benign or malignant, can occur practically everywhere in the body.

  **Neuroendocrine tumors**
  Neuroendocrine tumor arises from tissues which secrete hormones in the circulation in reaction to nerve communications. These tumors, which might produce more hormones than usual, can cause a wide range of symptoms.

- **Anticancer agents**
  Surgery, chemotherapy, and/or radiation therapy are the three major treatments for cancer. Chemotherapy employs low molecular weight molecules to specifically target and kill tumor cells or at least; stop them from growing. According to their mechanism of action and chemical structures anticancer agents are classified into following categories.

- **Alkylating agents**
  These substances are commonly referred as alkylating substances as they are responsible for DNA alkylation. The N7 position of guanine is the most common site for alkylation. The DNA backbone’s bases (guanine, thiamine, adenine, and cytosine) are alkylated. When DNA is alkylated, the alkylated regions become susceptible to the
cleavage which leads to the production of a single
strand. On the basis of structure Alkylating agents
are classified into following categories\textsuperscript{18}.

\textbf{Nitrogen mustard}

Nitrogen mustards are cytotoxic
organic compound having the functional
group chloroethylamine. They were the first
chemotherapeutic drugs used to treat cancer.
Nitrogen mustards are DNA alkylating agents that
are nonspecific. Meclorethamine, cyclophosphamide
(Fig. 1), chlorambucil and melphalan are the example
of this category\textsuperscript{19}.

\textbf{Nitrosourea}

Nitrosourea is a class of chemicals
composed of a nitroso (R-NO) group and urea. Nitrosourea chemicals are DNA alkylators that are
commonly employed in chemotherapy. Because
they are lipophilic and can pass the blood-brain
barrier, they can be used to treat brain tumors such
as glioblastoma multiforme. Common examples of
this class include carmustin\textsuperscript{20} (Fig. 2) and lomustin.

\textbf{Ethylene amine}

Thiotepa is the major examples of this
class, Thiotepa is a tertiary aziridine agents and it
is classified as a weak alkylator. Thiotepa, having
the formula \((C,H,N)_3PS\), is an organophosphorus
compound. Thiotepa (Fig. 3) introduces an alkyl
group into DNA. This procedure inhibits DNA from
being utilized in protein synthesis or the formation
of new cells, including cancer cells\textsuperscript{21}.

\textbf{Alkyl sulfonate}

Busulfan (Fig. 5) are the representative
of this category, chemically busulfan contains two
methyl sulfonate ethers binds with alkyl group on
both sides. When the busulfan undergoes hydrolysis,
methylsulfonate groups escape and carbonium ions
are created. This carbonium ions alkylate DNA,
disrupting the nucleic acid’s activity by interfering
with DNA replication and RNA transcription. Its
mechanism of action, particularly alklylation, which
results in intrasand guanine-adenine cross-
links. These cross-linking develop as a result of a
reaction called SN2 in which guanine N7 attacks
the carbon adjacent to the mesylate leaving group
nucleophilically. The cell dies because this form of
damage cannot be repaired by cellular machinery\textsuperscript{23}.
**Anti metabolites**

Metabolites are the chemical substances involved in the cellular metabolism. Antimetabolites are the chemical substances which take part in the cellular metabolism and inhibit the action of metabolites. Antimetabolites may cause DNA damage indirectly through misincorporation into DNA, which results in aberrant timing or advancement through DNA synthesis, or directly through changed function of enzymes involved in pyrimidine and purine synthesis. Antimetabolites further classified into following categories.

**Folate antagonist**

Folic acid is required in the synthesis of thymidylate and purine and ultimately for the production of DNA. Methotrexate (Fig. 6) is a folic acid antagonist acts by inhibiting DHFR (Dihydro folate reductase) enzyme. So, methotrexate is known as indirect inhibitor of thymidylate synthetase which enzyme involved in DNA synthesis. Methotrexate also effective in inhibiting glycinamide ribonucleotide transformylase which is the key enzyme for the synthesis of purine.

Pyrimidine analogue

Pyrimidine analogues are antimitabolites that disrupt the synthesis of nucleic acids. 5-Fluorouracil (Fig. 8) is a fluorinated pyrimidine analogue. 5-Fluorouracil is biotransferred into 5-fluoro deoxyuridylate which inhibits the enzyme thymidylate synthetase this enzyme is responsible for the conversion of uridine mono phosphate to thymidine mono phosphate. thymidine mono phosphate is an important component of DNA synthesis.

**Purine analogue**

Purine analogues are a class of drugs with identical structures but distinct modes of action, pharmacokinetics, indications, and side effects. Mercaptopurine (Fig. 7) and thioguanine belongs to this category Mercaptopurine is converted to thioguanosine acid in presence of enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT). Thioguanosine acid inhibits some enzymes which are responsible for the synthesis of purine.

**Natural products**

Natural products have been found to be a great and effective source of anticancer drugs. Natural products, an essential source for emerging therapeutic medications, are now being investigated as promising cytotoxic compounds and have shown an encouraging trend in preclinical studies, triggering a slew of novel cancer-fighting tactics and hastening clinical research. Following compounds belongs to this family.

**Plant products**

Vincristine (Fig. 9) and Vinblastine is an important derivative of this category. Both are very important drugs used in combination with procarbazine and prednisone. They are active against a variety of proliferating neoplasm. Vincristine and Vinblastine interfere with mitotic cycle they are also bind with β-tubulin (a microtubular protein) to form Drug-tubulin complex. This complex prevents its polymerisation and assembling of microtubules, which causes disruption of mitotic spindles. Due to this chromosome fails to move apart during metaphase That leads to arrest of metaphase and cell division inhibited.
Antibiotics

The antibiotics antineoplastic agent is a broad category of natural or semi synthetic compound that block DNA by inducing mutation in DNA strand or by inhibiting the enzyme needed for the DNA replication process. The antineoplastic antibiotics compound inhibits the topoisomerase, which enzyme responsible for maintaining proper DNA structure and transcription of RNA. Bleomycin, doxorubicin (Fig. 10) and daunorubicin is the common examples of this class30.

Miscellaneous

Aside from the above categories, certain other substances work as anticancer agents, such as cisplatin34 (Fig. 12), a platinum co-ordination complex which is hydrolysed intracellularly to release highly reactive residues that cause cross-linking of DNA and DNA damage. Mitotane35 (Fig. 12), often known as a miscellaneous agent, is a cytostatic antineoplastic drug. By interfering with DNA replication, this drug suppresses cell division and destroys the dividing cell.

Hormone

Hormone therapy is a method of cancer treatment in which certain hormones are removed, blocked, or added to the body. The kind of cancer and the depth that it spreads dictate the goal of hormone therapy. Sometimes the goal is to prevent cancer from returning following therapy. Alternatively, the goal could be to halt or reduce the progression of cancer. Prednisone (Fig. 11) and diethyl stilbesterol are mostly used hormones in this therapy31.

Enzyme

A variety of variables affect the expansion of cancer, complicating treatment. As the cancer spreads within the tissue, some enzymes or protein products within the cell can be up-or down-regulated. Enzymes that play important roles in cancer can be targeted for treatment32. There are various advantages of using amino acid degrading enzymes over traditional anticancer therapies. To begin with, amino acid enzymes have potent impacts on particular amino acid auxotrophic tumours. Second, the enzymes' side effect pattern is distinct, which is important for drug combinational therapy. Finally, important synthetases can be used as biomarkers to predict the therapeutic response. FDA approved L-asparaginase for the treatment of acute lymphoblastic leukaemia33.

Aromatase Inhibitors

Aromatase P-450, which catalyzes the conversion of androstenedione and testosterone into estrone and estradiol, is the main enzyme for the synthesis of estrogen. Breast cancer is promoted by estrogens in both premenopausal and postmenopausal women. However, breast cancer diagnoses are made in women who have beyond menopause, and the chance of developing the disease simultaneously increases with advancing age. Aromatase inhibitors significantly reduce the amount of circulating oestrogen by preventing estrogen production in extracellular tissues such as fat. Aromatase Inhibitors are an effective kind of targeted therapy for patients who have breast cancer with positive estrogen receptors (ER+). This is due to the enzyme aromatase, which catalyzes important processes in the production of estrogen. Aromatase inhibitors are more efficient than selective estrogen
receptor modulators (SERMs) because they block both the genomic and nongenomic activities of ER. There are many aromatase inhibitors available in clinical practice like Exemestane (Fig. 13) inactivates enzyme through pseudo-binding to aromatase. Formestane (Fig. 13) is an aromatase inhibitor that significantly reduces level of estrogen. Anastrozole (Fig. 13) binds reversibly to heme ion and reduces level of E1 and E2, Letrozole (Fig. 13) and many more.

Novel and effective anti-cancer agents

Due to their better safety and effectiveness compared with conventional chemotherapy agents, targeted therapy medication has grown into popular for cancer therapy. Since the Food and Drug Administration of the United States (FDA) authorised the initial tyrosine Kinase inhibitory agents, imatinib, for sale in 2001, an increasing amount of small-molecule targeted drugs for cancer therapy have been invented developed. By the end of 2020, the United States Food and Drug Administration (FDA) and China’s National Medical Products Administration (NMPA) had authorised 89 small-molecule target selective anticancer medications. An enhanced understanding of cancer biology pathways can be credited, at least in part, for the higher rate of novel anti-cancer therapeutic research. Due to acquired medication resistance, metastasis and recurrence frequently result in cancer mortality. Traditional chemotherapy, which includes alkylating drugs, antimetabolites, and mitotic inhibitors, is insufficient to treat the majority of malignancies and results in more aggressive, drug-resistant, and metastasizing tumours. Traditional cancer therapies have several unfavourable side effects. This has prompted research into novel compounds that operate on recognised new targets and may be used as monotherapy or in conjunction with currently established chemotherapies to treat cancer.

Following are the major anticancer targets and their inhibitors:

P-38 map kinase inhibitors

Gene expression and cell signalling are both controlled by a set of enzymes known as mitogen-activated protein kinases (MAPK). The three important members of the MAPK family are Extracellular Signal-Regulated Kinase (ERK), p38 MAPK, and c-Jun N-terminal Kinase (JNK). They are all engaged in three distinct signalling cascades. MAPKs become active when they are phosphorylated, and they can be controlled by both transcriptional and non-transcriptional mechanisms to change how the cell responds to different signals from outside the cell. In consideration to a stress-induced kinase, P-38 MAPK is essential for inflammatory reactions. A serine/threonine-protein kinase induced by cellular stress is the P-38 subgroup of MAPK. There are four isoforms of the p38 MAPK family known as α, β, γ, and δ. The α-isoform is the most studied enzyme and is thought to play a significant part in the signalling cascade of inflammatory events. Most inhibitors target both isoforms because the β isoform shares the most significant degree of sequence homology (about 74%) with the γ isoform. In addition to treating inflammatory conditions, P-38 MAPK inhibitors are also utilised to treat cancer, either alone or in conjunction with other chemotherapeutic drugs. An oral p38 mitogen-activated protein kinase (MAPK) inhibitor with immunomodulatory, anti-inflammatory, and anti-cancer activity. It inhibits p38 activity after administration, preventing p38 MAPK-mediated signalling. This may result in the inhibition of proinflammatory cytokine production and the induction of tumour cell apoptosis. The serine/threonine protein kinase p38 MAPK, which is frequently upregulated in cancer cells is involved in the production of a number of cytokines involved
in inflammation and cellular proliferation, including tumour necrosis factor and interleukin (IL) \(^1\) and \(^6\)\(^1\).

In clinical practise, many P-38 map kinase inhibitors are available such as Linalool (Fig. 14) a plant-derived isoprenoid involved in treatment of lung cancer, Pinocembrin (Fig. 14) can prevent cancer or reverse disease onset by delaying or stopping the growth of cancer cells. It has cytotoxic effects against colon, breast, cervical, gastric, lung, and prostate cancer cell lines, Puerarin (Fig. 14) is an isoflavone glycoside derived from Pueraria lobata. It causes cell death through modulation of different mechanisms like oxidative stress, inflammation and autophagy pathways. Tanshinone IIA (Fig. 14) is from the roots of Salvia miltiorrhiza that is used as a medicine in Chinese medicine (Danshen). This group of chemicals, which includes in particular, against breast, cervical, colorectal, gastric, lung, and prostate cancer cell lines, as well as leukemia, melanoma, and hepatocellular carcinoma, among others, Tanshinone IIA and I have demonstrated tremendous potential as anti-cancer compound\(^42\).

The human Polo Like Kinase family consists of five members: PLK1 to PLK5. One of these, PLK1, has received the greatest attention.\(^44\) PLK1 performs a variety of tasks in the spindle midzone and during abscission in addition to being engaged in cytokinesis, meiosis, spindle construction, chromosomal segregation, control of mitotic entrance and the G2/M checkpoint, coordination of the centrosome and cell cycle. It is required for precise cell division regulation and genomic integrity in mitosis, spindle assembly, and DNA damage response\(^46\). Previous research has found that it is overexpressed in the vast majority of human cancer patients. Many investigations have found that inhibiting its expression with kinase inhibitors, RNA interference (RNA), or antibodies can limit cancer cell proliferation and cause cell death\(^46\). As a result, PLK1 may be a promising target for cancer therapy.

Gjertsen and team in 2015\(^47\), have done research on the powerful and specific PLK1 inhibitor Volasertib (Fig. 15) It prolongs mitosis by causing centrosome fragmentation, abnormal spindle, and chromosomal misalignment as well as triggering the spindle assembly checkpoint. In addition to Volasertib, there are other inhibitors undergoing various stages of research and clinical testing like BI2356 (Fig. 15) is currently in clinical trial. It strongly suppresses c-Myc expression and induces apoptosis, Poloxin (Fig. 15) induces centrosome fragmentation and abnormal spindle and chromosome misalignment, which activate the spindle assembly checkpoint and prolong mitosis, Rigosertib (Fig. 15) is a benzyl styryl sulfone analogue. It is competitive non-ATP inhibitor of PLK1.
Hypoxia-Inducible Factor (HIF) Inhibitors

Tumor-induced hypoxia or VHL gene-inactivating mutations activate the hypoxia inducible factor signalling pathway. It is a transcriptional factor that regulates gene expression in hypoxia adaptation processes like angiogenesis and apoptosis, as well as genes involved in tumour formation, invasion, and metastasis. Tumor cells Induce hypoxia in various ways, including rapid metabolism and oxygen consumption, endothelial dysfunction, or interruption of oxygen transport due to mass effects on arteries. Tumor-induced hypoxia activates the hypoxia-inducible factor (HIF) signalling pathway, promoting tumour growth and invasion. HIF1-alpha and HIF1-beta are two subunits of the transcription factor HIF. In a hypoxic environment, HIF1-alpha levels rise in the cytoplasm. The nucleus contains HIF1-beta, which binds to HIF1-alpha to activate angiogenic pathways that aid in the cell’s adaptation to hypoxia.

From the following study, we found that inhibition of HIF is also helpful in treating cancer, many HIF inhibitors are undergoing various stages of clinical testing like Everolimus (Fig. 16), Temsirolimus (Fig. 16) Vorinostat (Fig. 16) is a HDAC inhibitor, PT2385 (Fig. 16). Temsirolimus is mammalian target of rapamycin. It binds to an intracellular protein (FKBP-12) and inhibits cell division.

Tyrosine Kinase Inhibitors

RTKs (receptor tyrosine kinases) are essential regulating signalling enzymes which control tumour development & invasion. RTKs are involved in a variety of clinical conditions, particularly cancer. Approximately 30% of RTKs (MET, KIT, FLT3 etc.) are mutated or overexpressed in various human malignancies. Oncogenic alterations or genetic duplications that affect the juxta membrane region of KIT and FLT3, which result in continuous stimulation of those receptors in absence of their ligand and are thus directly linked to the carcinogenesis process. FLT3 juxta membrane duplications induce continuous activation of receptors in fifteen to thirty percent of the acute myeloid leukaemia cases and sixty-five percent of gastric epithelial cancers. Autocrine stimulation or amplification of the EGFR, or epidermal growth factor receptor, has been linked to several types of solid tumours. Therefore, EGFR/ErbB-1 and ErbB-2 are elevated in breast, lung, and prostate malignancies, and the presence of them has been linked with higher aggressiveness and a bad prognosis.
In therapeutic trials with first generation epidermal growth factor receptor reversible inhibitors of ATP-binding sites (gefitinib and erlotinib in cancer patients), the use of receptor tyrosine kinase inhibitors (RTKIs) in non-small cell lung cancer (NSCLC) was reported. When compared to chemotherapy, these treatments increased patient survival by 50%. The second generation of Receptor Tyrosine Kinase Inhibitors includes irreversible inhibitors (afatinib and dacomitinib) with increased affinity for the EGFR kinase domain, which also inhibits other members of the HER family to which the EGFR belongs. In comparison to chemotherapy, afatinib doubles survival. Dacomitinib outlived gefitinib in a clinical trial.

An example of a COX-2 inhibitor is Celecoxib (Fig. 18) and Rofecoxib (Figure 18).

Cox Inhibitor

The Cyclo oxygenase (COX) enzymes serve a critical role in the biosynthetic process for important biological mediators known as prostanoids, which are generated from arachidonic acid (COX-1 and COX-2). For homeostatic regulation, such as control of renal blood flow, platelet aggregation, and gastric cytoprotection, COX 1's role is to provide and maintain an adequate number of prostanoid precursors. At inflammation locations and in many neoplasic cells, COX-2 expression is swiftly boosted or enhanced in response to pro-inflammatory stimuli (cytokines, hormones, growth factors, and hypoxia). Furthermore, it is well known that COX-2 is overexpressed in so many cancers, aiding in the development and progression of the illness by promoting cell growth, preventing apoptosis, and promoting neovascularization. Cancer therapy results COX2 inhibitor therapy for organs such as the lung, breast, colon, and prostate has been proven to reduce cancer risk by roughly 68%.

Vascular Endothelial Growth Factor (VEGF) Inhibitor

Vascular endothelial growth factor (VEGF) is a family of structurally and functionally similar protein molecules that includes the subtypes VEGFA, -B, -C, and -D, as well as placental growth factor. Many cancers, including colorectal cancer, breast cancer, lung cancer, and others, have elevated VEGF expression. The degree of VEGF expression correlates with microvessel density and metastatic dissemination in a variety of tumor types, including colorectal, breast, cervical, and melanoma. Because of its critical role in tumor angiogenesis and relationship to tumor development, VEGF has emerged as the most appealing therapeutic target for angiogenesis reduction. VEGF was identified as an endothelial cell-specific mitogen capable of causing healthy and pathological angiogenesis. It is the primary stimulus for angiogenesis, a process involving the ability of matching receptors to drive signaling pathways that increase endothelial cell proliferation and migration, as well as these cells' ability to destroy and reconstruct the stroma. As a result, VEGF and the receptor-mediated signaling pathways that it promotes are regarded as one of the most important therapeutic targets for the treatment of a wide range of malignancies. Anti-VEGF-based antiangiogenic medications are now often employed to treat different kinds of cancer.
CONCLUSION

Worldwide, there are 3500 deaths per million people attributable to cancer each year. Since 1991, cancer death rate has been steadily decreasing, resulting in a 33 percent overall reduction with approximately of 3.8 million cancer deaths avoided. There are several chemo preventive drugs that treat a variety of cancers, but they all have undesirable side effects, which restricts how widely they may be used. Even though over 1500 anticancer treatments are now in the process of being created, and even though over 500 of those therapies are currently going through clinical trials, there is an immediate need to produce medicines that are both more effective and less hazardous. This issue is dealt with in an efficient manner throughout this review study. In this overview, different forms of cancer, traditional chemotherapeutic drugs, novel targets, and inhibitors of those targets are discussed. This evaluation has the potential to serve as a foundation for future clinical treatment and research.

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Conflict of interest

Authors do not have any conflicts of interest to declare.

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