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Review Article

Recent developments in the search for anticancer drugs: A review

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Abstract

Uncontrolled cell proliferation causes cancer, which is characterized by the growth of an unusually large tumor that first appears as a localized illness but has the potential to spread and affect other organs or critical functions. One of the most lethal diseases in modern history, cancer claims the lives of countless individuals annually. The efficacy of treatment for this condition has been impacted by socioeconomic circumstances, geographical differences in the disease, and the impact of easily accessible medical services. Finding new anticancer drugs has been a recent focus of research, and this study aimed to summaries previous articles on the subject. This review classifies a large number of findings into several categories, including anticancer therapeutic targets, chemical compounds with in vivo or in vitro cytotoxic drug discovery, breakthroughs derived from plants, and repurposing. Using PubMed Central, Google Scholar, and Science Direct, the previously published literature on anticancer drug discovery advancements from March 20 to May 12 was meticulously culled from publications. Items that I thought were relevant and up-to-date (2017–2023) were incorporated. This review summarizes recent advances in the hunt for anticancer medications by drawing on a variety of academic sources. This issue encompasses various aspects such as plant-derived cancer advancements, pharmaceuticals repurposed for cancer treatment, and prospective and clinically demonstrated pharmacological targets for anticancer drug binding. therapy, followed by a discussion of developments in innovative chemical compounds used in cancer therapy

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1.Introduction

Cancer is a disease characterized by unchecked cell proliferation, which in turn causes tumors to grow abnormally and pose a threat to other vital organs or systems, reducing their ability to live.[1] A number of factors, such as alterations in DNA, environmental contaminants, dietary poisons, viruses, chemicals, and ionizing radiation, interact to produce cancer. is why it's seen as a complex disease.[2] Two genetically identical cells are generated every time a cell divides thanks to a variety of cell cycle control mechanisms that have evolved to be quite stringent.[3] Among the most lethal diseases in modern history, cancer claims the lives of countless people annually. Various socioeconomic factors, as well as the disease's global variations and the influence of available medical facilities, have impacted the right treatment of this sickness.[4] According to the latest cancer data, there will be 10 million deaths and 20 million new cases of cancer worldwide in 2023. Over the next two decades, the number of cancer cases will increase by more than 60%, putting further strain on healthcare systems, communities, and individuals. Between 2000 and 2016, researchers in Ethiopia estimated that 50,913.5 (or 95%) deaths occurred in the country due to cancer. The mortality rate was 93.5 per 100,000 patients, adjusted for age, and 49.7 per 100,000 patients, with the majority of deaths being female. The number of cancer cases has soared to record levels, perhaps caused by people living longer. Because of this, the pharmaceutical industry has poured a lot of money into this field of medicine. Despite these efforts, cancer medication research is still a very difficult area to work in, and therapeutic breakthroughs have not led to the anticipated clinical advantages.[5]

But pharmaceutical companies have kept making medications since the early 1900s, even if they are extremely expensive. cost-effectiveness ratio, taking into consideration the improved understanding of the disease's[6,7] physiopathology An assortment of cytotoxic medications, hormones and hormone antagonists, immunomodulators, antibiotics, antimetabolites, and plant extracts are among the many groups of anticancer drugs created by pharmaceutical corporations.[8,9] Problems with these chemotherapies include cytotoxicity, lack of selectivity, induction of multidrug resistance, and proliferation of stem-like cells ($8,9$).10Hope for the creation of more efficient treatments has been bolstered by the identification of new molecular targets. Finding new anticancer drugs has been a recent focus of research, and this study aimed to summaries previous articles on the subject. This review classifies a large number of findings into several categories, including anticancer therapeutic targets, chemical compounds with in vivo or in vitro cytotoxic drug discovery, breakthroughs derived from plants, and repurposing.[5,10] Finding new anticancer drugs has been a recent focus of research, and this study aimed to summaries previous articles on the subject. This review classifies a large number of findings into several categories, including anticancer therapeutic targets, chemical compounds with in vivo or in vitro cytotoxic drug discovery, breakthroughs derived from plants, and repurposing.

1.1. Exploration methodology

Data from earlier studies on the identification of anticancer medications were collected from journals between March 20 and May 12 using PubMed

Central, Google Scholar, and Science Direct.

In order to facilitate referencing, the literature was precisely retrieved, arranged according to the publication date and topic's vicinity, and then immediately cited from the works.

2.Resources and Techniques

In this review, the reviewer conducts searches using a personal computer and additional devices on websites including Science Direct, PubMed Central, and Google Scholar.

2.1. Searching for outcomes

Upon utilizing the aforementioned techniques to search and filter recently released literature, I discovered that a significant number of the publications discussed the latest developments in the field of anticancer drug research. Three main categories comprise these results:

anticancer medication targets and biomarkers; studies on newly developed cytotoxic drugs in vivo and in vitro; and advancements obtained from plants. Furthermore, included are developments in medication repurposing. Also included are research on drug repurposing, including those involving anticancer drugs that have been approved, stopped, and shelved. Studies on gene therapy, immunotherapy, phytomedicine, and electrochemotherapy are also mentioned.

3.Oversight of Anticancer Drug Research in General

Anticancer medication discovery and development has been fraught with difficulties for academics and pharmaceutical corporations owing to the task's complexity, cost, time, and difficulty.Because they miss certain cancer cells,[11] hand-administered treatments are not only risky but also very difficult fact that manufacturers are working on anticancer medications does not change this.[12,13] Therefore, modern in silico technologies greatly facilitate the development of selective small-molecule medicines through the design and construction processes.[14] intriguing.14 Artificial intelligence (AI) has just emerged as a strong and promising technology that can design anti-cancer therapies more quickly, cheaply, and effectively than CADD.[11] The development of more alluring medicinal molecules and the acceleration of the search for novel therapeutic compounds are both made possible by artificial intelligence. Starting with target identification, the process of discovering new anti-cancer drugs involves screening promising compounds based on structure, ligand, or fragment information. Large compounds are designed de novo, anti-cancer drugs are repurposed, and accurate reaction predictions can be made.[15,16] Utilizing AI-based sophisticated technology, or before CADD, helps in the development of anticancer medications. which considers the toxicity and effectiveness of drugs while also being discovered through natural products or synthetic means. Using promising targets for medication repurposing has also gained popularity recently.[17,19] Nevertheless, there are disadvantages to cancer immunotherapy, including delivery technique problems, resistance, and the capacity of cancer cells to elude the immune response.[20] Recent developments suggest that there may be solutions to some of the problems with nanoparticles employing nanocarriers as vehicles.[21] Nanoparticles have unique properties that make them useful in the treatment of

cancer. These properties include reduced toxicity, enhanced permeability, enhanced stability, precise targeting, and retention impact.[22]

4.Advancements in Anticancer Drug Targets and Biomarkers Lately

Targeted therapy is the key to improving cancer survival rates while decreasing treatment-related side effects. Both overall survival and progression-free survival were significantly improved in patients who got matched targeted therapy compared to those who did not.[23] The therapy of cancer has made progress with the identification of multiple therapeutic targets.

Most of the targeted agents were ineffective or poisonous, rendering them useless. Research into the molecular pathophysiology of cancer and new advances in molecular biology pose a challenge to efforts to pinpoint treatment targets that may lead to the disease's complete eradication.[24]

4.1.Kinases as objectives

The active site of the target enzyme is directly impacted by a class of anti-cancer drugs called kinase inhibitors, which stop kinase activity. There are an estimated 2000 kinases, either tyrosine- or serine/threonine-specific, linked to each other in the human genome.[24] The oncology community was first introduced to imatinib, then bosutinib, sorafenib, and sunitinib. Despite sharing the similar mechanism of action—competitive ATP inhibition at the tyrosine kinase catalytic binding site—they vary in range of targeted kinases, pharmacokinetics, and substance-specific side effects.[25]

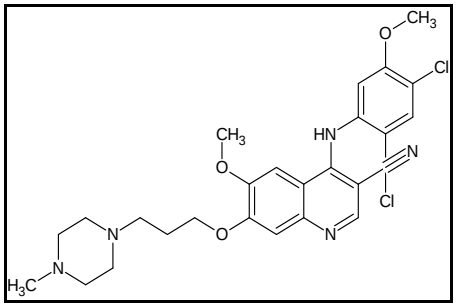

Figure 1 Bosutinib

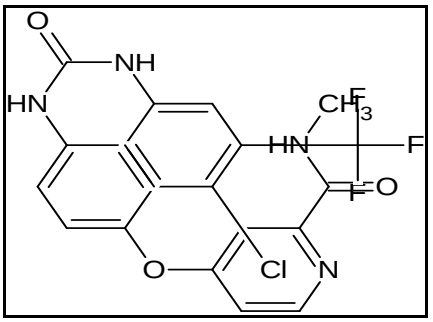

Figure 2 sorafinib

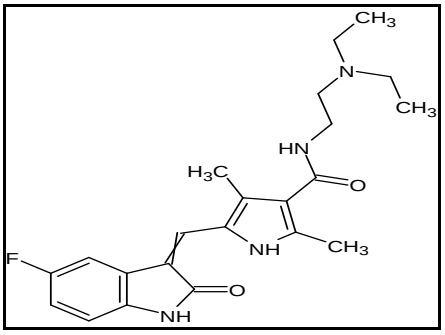

Figure 3 Sunitinib

4.2. focusing on tubulin or microtubules

Microtubules are an important part of the cytoskeleton in eukaryotic cells, and they are formed when the globular protein tubulin, which has a molecular weight of 52 KD, polymerizes. At every stage of cell cycle, microtubules are constantly lengthening and shortening. When compared to normal cells, cancer cells divide and multiply at an accelerated rate. Because of the critical role they play in cell proliferation and division, researchers are looking into the development of

microtubule-targeting drugs for the treatment of cancer. Consequently, one of the main targets for the development of anti-cancer drugs is now tubulin. Studies of the structure-activity relationship have been conducted, and several tubulin-targeting compounds have been synthesized in an effort to uncover and develop safer and more effective therapeutic candidates.[24,26]

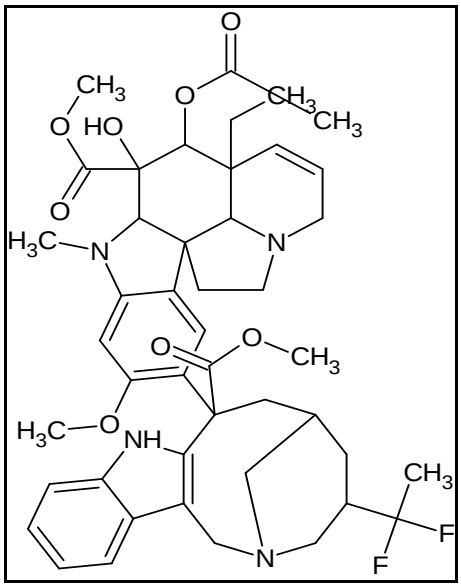

Figure 4 Vinflunine

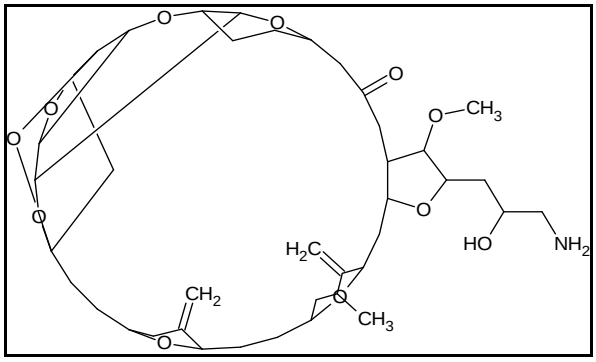

Figure 5 Eribulin

4.3.Vascular target agents

Most commonly used as cancer treatments, vascular targeting agents (VTAs) are designed to directly target the vasculature of the tumor in order to stop the growth and development of the tumor. Bloodborne medicine is now widely available, making it a viable therapy option for cancer. Tumor cells divide quickly, therefore a constant supply of nutrients and oxygen is required. As a result, the formation, spread, and metastasis of cancers depend on the expansion of blood artery networks. Tissue-damaging agents (VDAs) have the ability to obstruct blood supply to malignancies.[27,28]

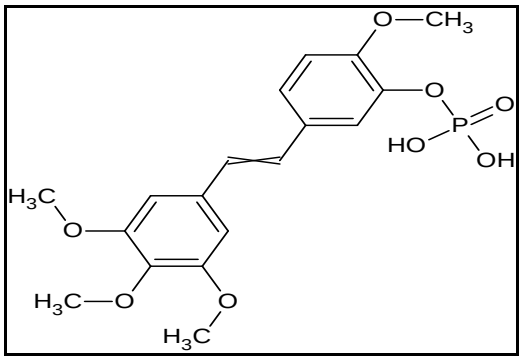

Figure 6 Fosbretabuli

4.4. Inhibitors of Angiogenesis

Angiogenesis inhibitors are a new class of drugs developed to block the process of tumour vascularization. Uncontrolled expression of VEFG-A contributes to tumour development, invasion, and metastasis. At this time, treatments that aim to suppress VEGFR2 also target VEFG-A.28Treatment of non-small-cell lung cancer (NSCLC) involves the use of angiogenesis inhibitors, like ramucirumab and bevacizumab. These medications work by blocking VEFGs.[29]

4.5. Monoclonal antibodies

A new class of drugs called angiogenesis inhibitors is now in development with the goal of preventing tumour vascularization. When tumours develop, invade, and metastasise, it's because VEFG-A is overexpressed. At this time, inhibitors of both VEGFR2 and VEFG-A aim to block VEFG-A. Bevacizumab and ramucirumab

are examples of angiogenesis inhibitors (AIs) used to treat non-small cell lung cancer (NSCLC). Inhibiting VEFGs is the goal of these drugs.[29]

5.Latest Progress in Repurposing Drugs to Find Novel Anticancer Treatments

Drug repurposing, also known as drug repositioning, is a strategy that considers diseases other than the one for which a treatment has already been approved.[30,32]

5.1. Antiplatelet Agents

The main purpose of aspirin is to treat cardiovascular disorders by acting as an antiplatelet agent, even if its clinical use as an anticancer drug has grown and consistent use of the drug is linked to a decreased risk of breast cancer. Breast cancer may be treated with combination therapy using aspirin and PI3K inhibitors.

5.2. NSAIDs drugs

Recent in vivo data point to diclofenac's ability to halt the development of pancreatic tumors in mice. Analysis of surgically removed Tumour tissue revealed that diclofenac therapy promoted apoptosis and decreased angiogenesis.

All cancer cells reacted favorably to the treatment of melanoma cells with a combination of diclofenac and kinase inhibitor sorafenib.[34] Celecoxib, a selective COX-2 inhibitor, also reduced breast cancer cell growth and Tumour development in in vivo rat models. Researchers discovered that Tumour cell invasiveness and COX-2 expression levels were mutually necessary for growth suppression.[35]Mesalazine may also have anti-cancer effects in cases of stomach, colorectal, colon, and breast malignancies, among others.[36]

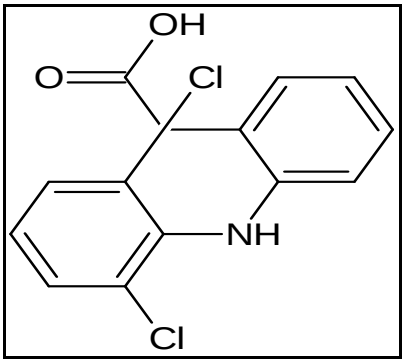

Figure 7 Diclofenac

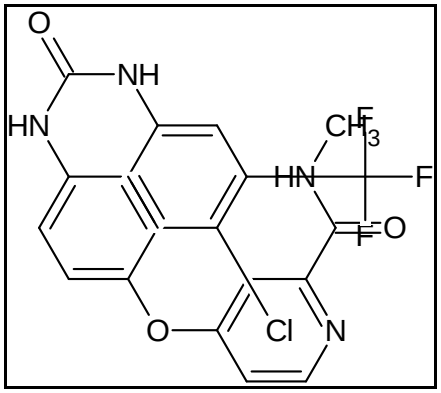

Figure 8 Sorafinib

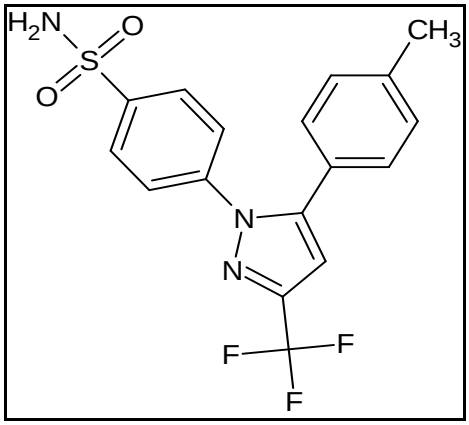

Figure 9 Celecoxib

5.3.Antidiabetic agents

Metformin is the first drug used to treat type 2 diabetes mellitus. It is taken orally. Many cancer types have demonstrated its anti-neoplastic action, including breast, lung, prostate, pancreatic, endometrial, and lung cancer.[37] Thiazolidinediones (TZDs) have been found to be a powerful lead in the treatment of prostate and breast cancer through a number of preclinical and clinical

investigations. The main ingredients of this drug are troglitazone, rosiglitazone, and pioglitazone.[38]

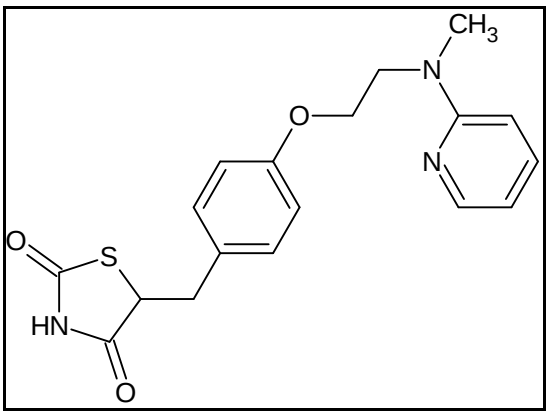

Figure 10 Rosiglitazone

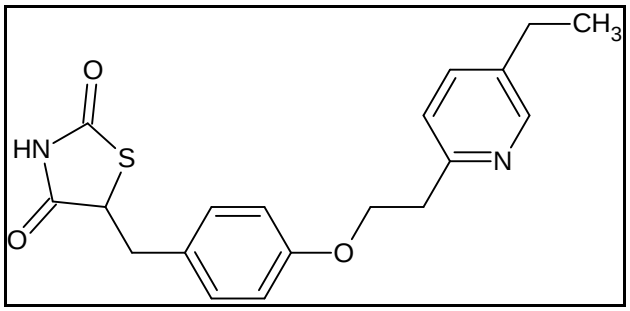

Figure 11 Pioglitazone

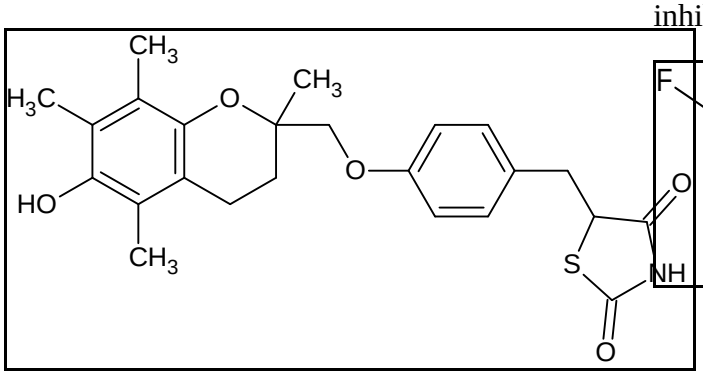

Figure 12 Troglitazone

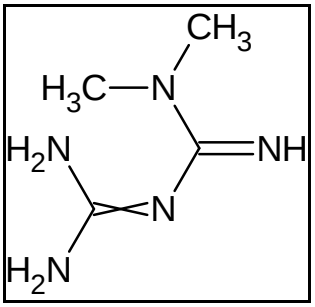

Figure 13 Metformin

5.4.Anthelmintic agents

Flubendazole and albendazole are examples of pleiotropic benzimidazole anthelminthics. These medications have a long history of safe human use, are inexpensive as generics, and are now being considered as a potential therapeutic option.

Several studies in the lab and in humans have shown that these benzimidazoles have a wide range of effects, including inducing cell death and M1 polarization, disrupting microtubules, acting as immune checkpoints, inducing hypoxia-inducible factor, inducing epithelial-mesenchymal transition, promoting cancer stemness, and inhibiting multidrug resistance protein.[30]

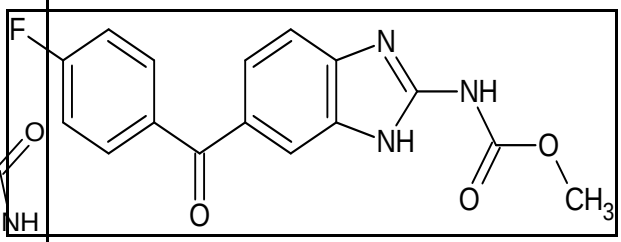

Figure 14 Flubendazole

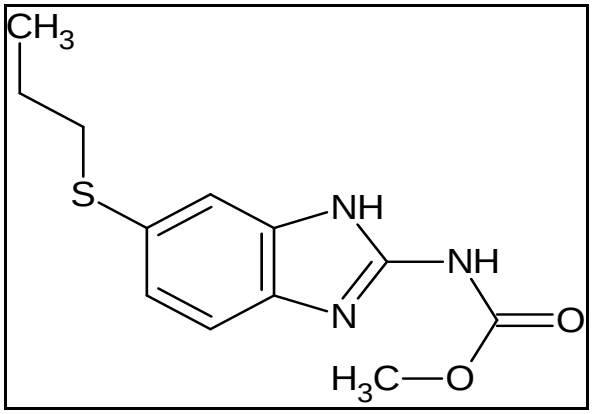

Figure 15 Albendazole

5.5. Antipsychotic agents

Results from multiple studies showing a decreased incidence of prostate, colon, and rectal cancer[39] in patients treated with antipsychotic medications for mental disorders including schizophrenia suggest that these treatments may have anti-cancer properties. Aripiprazole is prescribed to patients suffering from schizophrenia. Cancers of the colon, glioma, and stomach all have their Tumour growth and cell division slowed down by this.[40,41] Sertindole is an attractive potential medicine for the treatment of stomach and breast cancers.[42] Valproic acid, a popular neuroleptic medication for migraines, bipolar disorder, and epilepsy, has been discovered to employ epigenetic mechanisms, such as the regulation of histone deacetylases,[43] to produce cellular differentiation, restrict angiogenesis, and further diminish Tumour cell proliferation. Evidence suggests that phenothiazines slow Tumour cell proliferation, induce Tumour stem cells to differentiate, and block mitochondrial DNA polymerase. For the treatment of bipolar disorder, schizophrenia, and Tourette syndrome,[44] olanzapine affects the cholesterol homeostasis, which in turn kills cancer cells. Proof exists that SSRIs reduce the rate of Tumour cell division and, eventually, induce their death.[45]

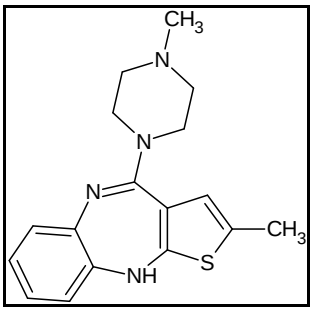

Figure 16 Olanzapine

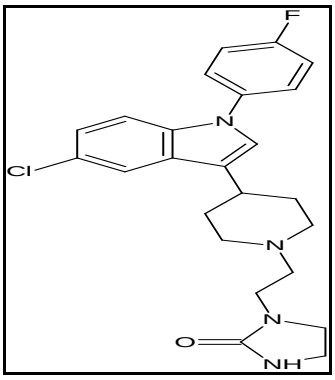

Figure 17 Sertindole

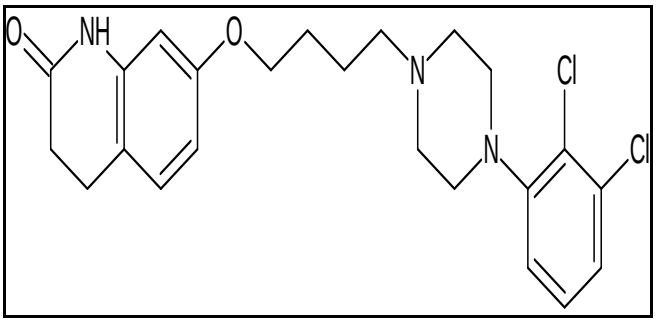

Figure 18 Aripiprazole

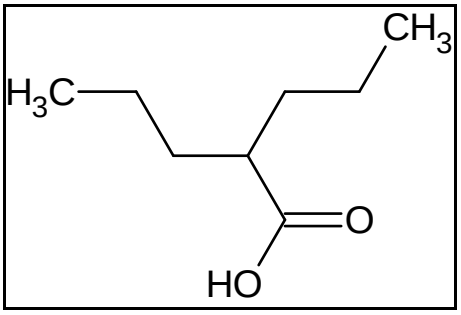

Figure 19 Valproic Acid

5.6. Antiviral drugs

Zidovudine, a reverse transcriptase inhibitor, was the first medication authorised to help with HIV infection. Its anti-cancer capabilities have been demonstrated in several cancers, including as pancreatic cancer, leukemia, and Kaposi sarcoma. A herpes simplex virus medication called zidovudine has demonstrated anti-cancer effects by reducing chemoresistance in a manner similar to this. Ritonavir has been found to increase cell death and decrease growth and division in cancer cells of the ovary, pancreas, and breast. Nearly half.[46,47]

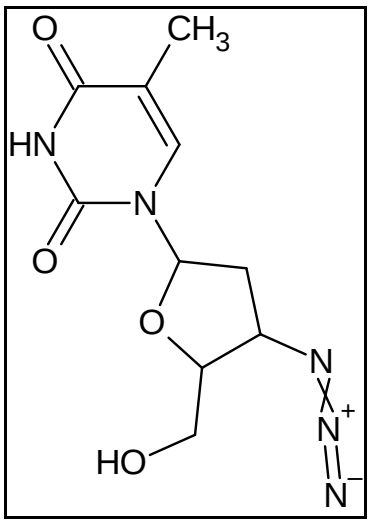

Figure 20 Zidovudine

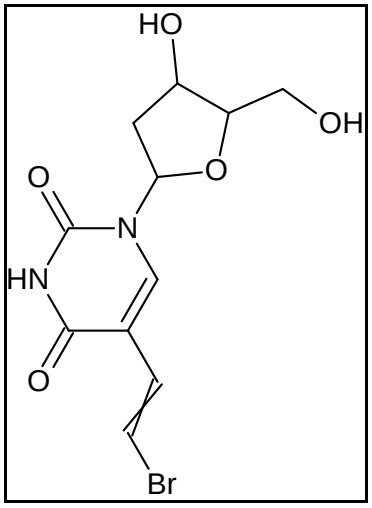

Figure 21 Brivudine

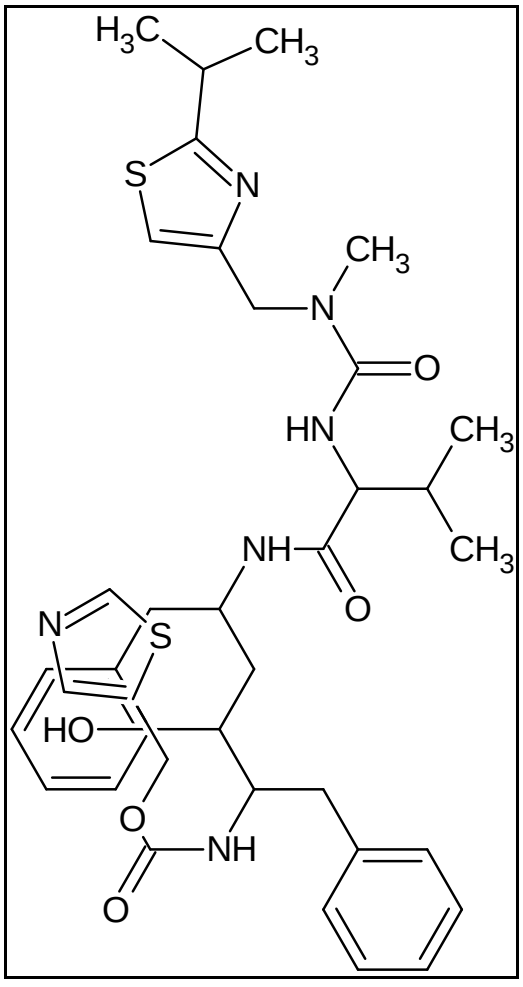

Figure 22 Ritonavir

5.7. Antifungal agents

It has been demonstrated that the antifungal medication itraconazole HUVECs, glioblastoma cells, endometrial cancer

cells, and melanoma cells all had their AKT/mTOR signaling pathways inhibited. It eliminates P-glycoprotein-induced chemoresistance, stops cancer cells from forming new blood vessels (angiogenesis), and controls the Hedgehog signal transduction pathways.[48] Furthermore, melanoma, prostate, breast, and hepatocellular carcinoma were among the cancers that ketoconazole showed anti-cancer effect against. It is generally more acceptable and has fewer adverse effects, but it also efficiently prevents the synthesis of exosomes in prostate cancer cells.[49]

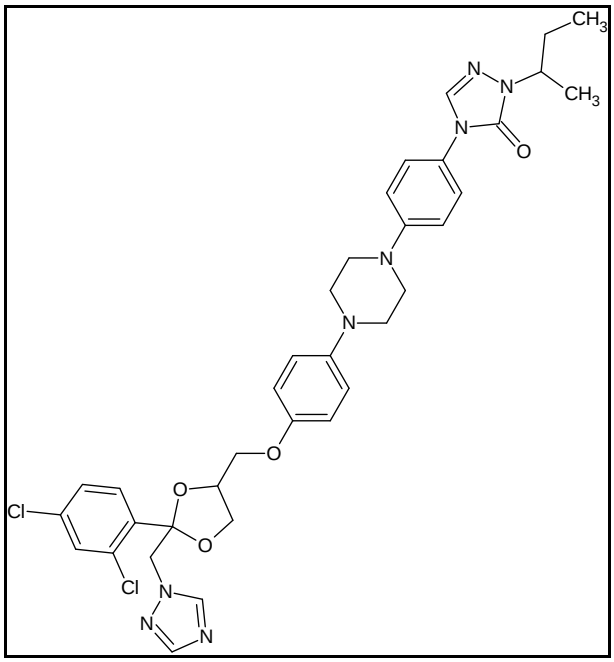

Figure 23 Itraconazole

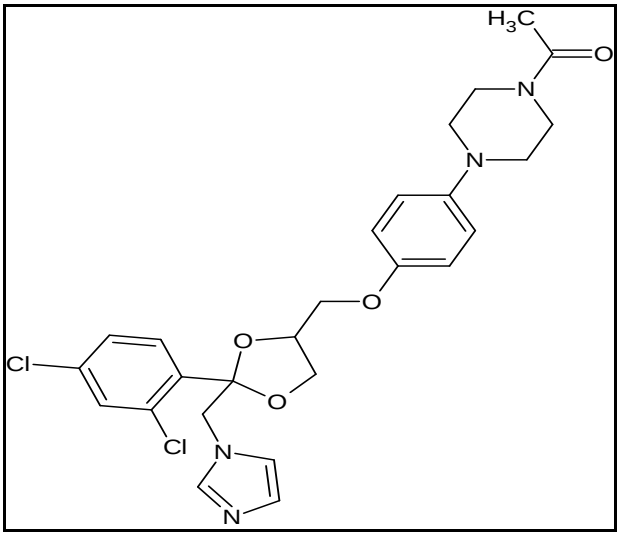

Figure 24 Ketoconazole

5.8. Antibacterial agents

Doxycycline induces G0/G1 arrest and blocks matrix metalloproteinase, two mechanisms by which it suppresses the development of colon cancer cells when combined with a COX-2 inhibitor. Doxycycline targets breast cancer cells by preventing them from acquiring a stem cell characteristic and mitochondrial biogenesis. Research has shown that doxorubicin is an effective treatment for breast cancer. Genomic replication was halted as a result of intercalating breaks into the DNA.[50,51]

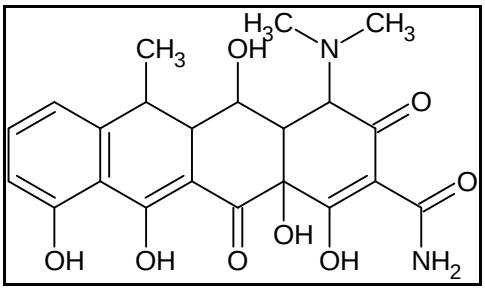

Figure 25 Doxycycline

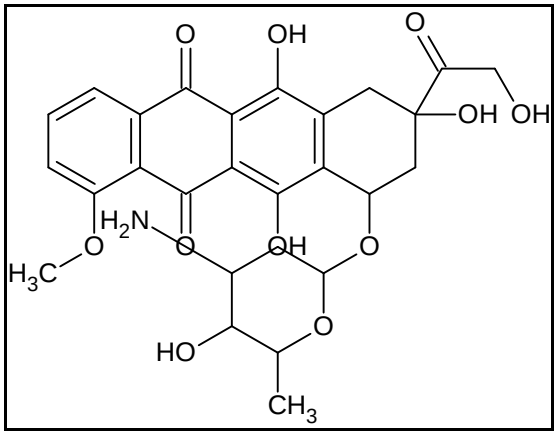

Figure 26 Doxorubicin

5.9. Heterometallic substances

Despite the widespread use of platinum-based drugs in medical therapies, interactions are the cause of their toxicity. Despite the widespread use of platinum-based drugs in medical therapies, their toxicity is caused by interactions between platinum and sulfur-containing biomolecules, such as thiols and thioethers.[51] The efficacy of these medications is consequently diminished. In order to address the side effects of platinum-based drugs, scientists are working on novel methods to create heterometallic complexes.[52] These complexes will feature metal centers with specific coordination geometry, kinetic properties, affinity, and reactivity towards nucleophiles that are important in biology.[53] The future of pharmaceuticals based on heterometallic compounds is brighter than that of drugs based on platinum, and they also offer the added benefit of decreasing toxicity. Platinum, gold, and titanium are more prevalent among the several promising heterometallic-based compounds being researched for cancer treatment.[54] plus connecting platinum to sulfur-containing biomolecules such as thiols and thioethers. The efficacy of these medications is consequently diminished. In order to address the side effects of platinum-based drugs, scientists are working on novel methods to create heterometallic complexes. These complexes will feature metal centers with specific coordination geometry, kinetic properties, affinity, and reactivity towards nucleophiles that are important in biology. The future of pharmaceuticals based on heterometallic compounds is brighter than that of drugs based on platinum, and they also offer the added benefit of decreasing toxicity. Platinum, gold, and titanium are more prevalent among the several promising heterometallic-based compounds being researched for cancer treatment.[55,56]

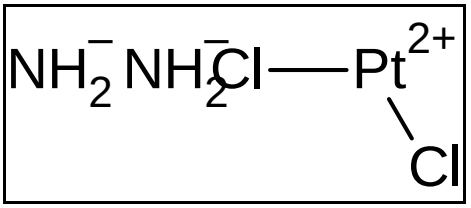

Figure 27 Cisplatin

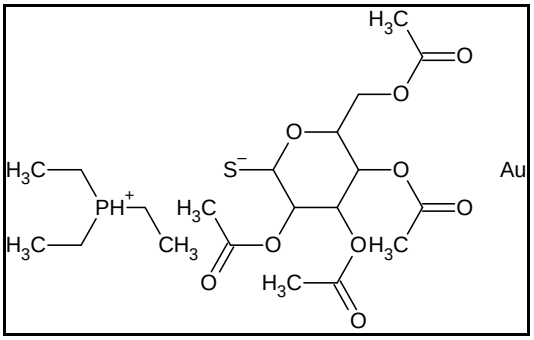

Figure 28 Ridaura

Significant anticancer activity has been observed through the synthesis and characterization of several novel heterocyclic compounds, such as thiazolidin-4-ones, 1,3,4-thiadiazoles, and thiazoles bearing thymol under mild conditions. The compounds' IC50 values range from 7 to 19 M against a panel of

human cancer cell lines.[57] Pyrazole is a five-membered ring with two adjacent nitrogen atoms in its structure. Because of its existence in many natural substances, it has been suggested as a strong contender in the pharmacological context with an intriguing therapeutic target covering a broad spectrum of biological activities.[58] Beyond concerns about the potential for heterocyclic chemicals to treat cancer, in vitro investigations have lately demonstrated advancements in the utilization of bisheterocyclic compounds as effective anticancer therapies.[59]

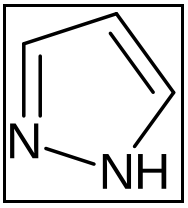

Figure 29 Pyrazole

6.Conclusion

Cancer has been a major focus for scientists and pharmaceutical corporations since the discovery of nitrogen mustards. Unfortunately, the disease's lack of selectivity, efficacy, side effects, and metastatic nature makes successful therapy challenging, even though there are many other medicines available. Thanks to recent developments in molecular biology and a deeper comprehension of cancer's molecular pathogenesis, scientists are concentrating on potential treatment targets that could lead to the complete eradication of the illness. The latest extracts from this article offer a historical overview of anticancer medication development. Recent developments in drug target and development have allowed researchers to make more informed therapy choices with better tolerance and less toxicity. Many pharmacological targets have been identified through various academic investigations with the goal of making cancer treatments more effective while reducing their toxicity. Here are the top domains of kinase, micro tubulin, vascular targeting, angiogenesis, and monoclonal antibodies for cancer treatment. To cut costs, save time, and find new uses for drugs that have already been approved for one ailment, researchers explore additional potential uses for these drugs. Medications that contain antipsychotic, antiplatelet, anti-inflammatory, antibacterial, or antidiabetic properties are some examples of repurposed medications. To find novel classes of anticancer medicines with novel mechanisms of action, phytochemical discovery has emerged as a key strategy. It is possible that quercetin, ginseng, artemisinin, and curcumin can fight cancer. Natural chemicals are superior and more effective chemotherapeutic medicines, though. Modern methods for reducing the side effects of chemotherapy have shown promising anticancer results in the form of metal-centered heterometallic complexes with heterocyclic and bis-heterocyclic compounds such as thiazolidin-4-ones, 1,3,4-thiadiazoles, and thiazoles.

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