World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

ANTINEOPLASTIC AGENTS FROM NATURAL SOURCES

Arup Kumar Maity*, Ashrubindu Bhunia and Dr. Beduin Mahanti

School of Pharmacy, Techno India University, Sector-V, EM-4/1, Salt Lake City, Kolkata-700091, West Bengal, India.

***Corresponding Author: Arup Kumar Maity**
School of Pharmacy, Techno India University, Sector-V, EM-4/1, Salt Lake City, Kolkata-700091, West Bengal, India.

Article Received on 21/03/2021 **Article Revised on 11/04/2021** **Article Accepted on 01/05/2021**

ABSTRACT

Cancer may be a multistep method and characterized by irregular proliferation of cells. Usually, these cells invade and destroy the traditional cells, so making associate imbalance within the body. Cancer is caused because of numerous factors like tobacco consumption, exposure of body to chemicals, dietary factors and environmental factors. Typical medication for treatment of cancer has many impacts on healthy cells. There's additionally a problematic issue of increase in tumor resistance to the present therapeutic agents. Because of this, there's a good have to be compelled to fight this malady with more practical medication. Natural product plays a very important role in fight against cancer and provides a valuable entry for the utilization and investigation of latest therapeutic agents. Healthful plants represent an honest supply of discovery and development of anticancer agents. Healthful plants contain many biologically active compounds that enable them to cure cancer. They contain numerous secondary metabolites that embody Alkaloids, flavonoids, phenolic, carotenoids etc. Edges of medication from plant origin over synthetic (chemical) drugs have accrued the importance of healthful plants within the field of attention. Varied healthful plants area unit identified to possess antineoplastic activity. Phytocompounds from these plant sources will forestall cancer initiation, promotion and progress by exerting anti-oxidant effects that mediates by the combination the combination, Nrf2 and AP-1signal pathways. Overall, this chapter provides a comprehensive repository for the scientific community operating to develop new and improved medicines for cancer that poses serious threat to world all across the world.

KEYWORDS: Anticancer, Medicinal plants, Phytocompounds, Anticancer activity.

INTRODUCTION

Antineoplastic agents are a group of specialized drugs used primarily to treat cancer (the term "neoplastic" refers to cancer cells). Cancer is a class of diseases in which a group of cells display the traits of uncontrolled growth, invasion and sometimes metastasis.

Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth. Complex interactions between carcinogens and the host genome may explain why only some develop cancer after exposure to a known carcinogen. New aspects of the genetics of cancer pathogenesis, such as DNA methylation, and microRNAs are increasingly being recognized as important. Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments. Tumor suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.[1]

Throughout history, natural products have played a dominant role in the treatment of human ailments. The associations of salicylates with the willow and quinine with cinchona are renowned examples; similarly, the legendary discovery of penicillin transformed global existence. In addition, traditional remedies, largely based on terrestrial plants, still dominate therapeutic practices throughout the world, and natural products comprise a large portion of current-day pharmaceutical agents, most notably in the areas of antibiotic and cancer therapies. For the treatment of cancer, early diagnosis and definitive tumor eradication through radiation therapy or

surgical resection offer greatest hope. However, when dealing with malignant, metastatic disease, it is generally necessary to resort to chemotherapy. As described herein, many of the meaningful advances that have been realized for the treatment of cancer are directly correlated with the discovery of natural product drugs.

In an ideal world, cancer chemoprevention would work as well as vaccines for the prevention of human ailments. Although this has yet to be accomplished, proof of principle has been established by seminal clinical trials conducted for the prevention of breast cancer with tamoxifen, and more recently with tamoxifen relatives such as raloxifene, and a separate class of aromatase inhibitors. Agents such as finasteride have shown promise for the prevention of prostate cancer. In terms of drugs under investigation, as is the case with cancer chemotherapeutic agents, natural products have played a critical role in cancer chemoprevention studies. An overview is presented herein.[2]

CANCER CHEMOTHERAPEUTIC AGENTS DERIVED FROM TERRESTRIAL PLANT: Over 60% of the current anticancer drugs were derived in one way or another from natural sources. Nature continues to be an abundant source of biologically active and diverse chemotypes, and while relatively few of the actual isolated natural products are developed into clinically effective drugs in their own right. Plants have been primary sources of natural product drug discovery, and in the anticancer area, plant-derived agents, such as Vinblastine (VBL) and vincristine (VCR), etoposide, paclitaxel (Taxol ®), docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available. Nevertheless, many suffer from the liabilities of poor solubility in aqueous media and significant toxic side effects. Thus, there continues to be considerable research devoted to diminishing the impact of these factors, and numerous analogues and prodrugs of these agents have been synthesized, and methods devised for increasing aqueous solubility and targeting specific tumors. The goals of using plants as sources of therapeutic agents are.

- To produce bioactive compounds of novel or known structures as lead compounds for semisynthetic to produce patentable entities of higher activity and/or lower toxicity, e.g., metformin, nabilone, oxycodon (and other narcotic analgesics), which are based, respectively, on morphine, taxol, podophyllotoxin, etc.
- To use agents as pharmacologic tools, e.g., lysergic acid diethylamide.
- To use the whole plant or part of it as a herbal remedy, e.g., cranberry, garlic, ginkgo etc.
- To isolate bioactive compounds for direct use as drugs, e.g., digoxin, morphine, reserpine, vinblastine, vincristine, etc.

DEVELOPMENT OF ANTICANCER DRUGS FROM PLANTS: It is estimated that there are roughly 500,000 higher flowering plant species occupying terrestrial habitats. A large number of species have only been very superficially examined for their pharmacological and medical application. Less than 1% of these species has been thoroughly investigated for their potential use as novel therapeutic agents.[3]

Traditionally, cancer drugs were discovered through large-scale screening of synthetic chemicals against animal tumor systems, primarily murine leukemia's. The agents discovered in the first two decades of cancer chemotherapy (1950-1970) largely interacted with the DNA or its precursors, inhibiting the synthesis of new genetic material or causing irreparable damage to DNA itself. In the area of cancer treatment, many claims have been made for the beneficial effects of plants. Drug discovery from medicinal plants has played an important role in the treatment of cancer. Of all available anticancer drugs between 1940 and 2002, 40% were natural products per se or natural product-derived with another 8% considered natural product mimics.

CLASSIFICATION OF ANTINEOPLASTIC AGENTS: Antineoplastic agents are also traditionally divided by their origin or mechanism of action. The main groups include.

1. Alkylating and alkylating-like agents
2. Antimetabolites
3. Antitumour antibiotics
4. Plant alkaloids
5. Hormonal agents
6. Miscellaneous agents

1. Alkylating and alkylating-like agents: - Classic alkylating agents interfere with DNA replication by crosslinking DNA strands, DNA strand breaking, and abnormal pairing of base pairs. They exert their lethal effects on cells throughout the cell cycle but tend to be more effective against rapidly dividing cells. Because alkylating agents are active against cells in G0, they can be used to debulk tumours, causing resting cells to be recruited into active division. At this point, those cells are vulnerable to the cell cycle-specific agents. These agents are active against lymphomas, Hodgkin's disease, breast cancer, and multiple myeloma.

Major toxicities occur in the haematopoietic, gastrointestinal and reproductive systems. Individuals treated with these agents are also placed at a higher risk of developing secondary malignancies. Examples include Cyclophosphamide, Ifosfamide, Chlorambucil, Busulfan and Melphalan. Another subgroup of alkylators called Platinum-containing compounds includes agents such as Cisplatin, Carboplatin and Oxaliplatin. Their cytotoxic properties also extend to alteration of the cell membrane transport systems and suppression of mitochondrial function.

2. Antimetabolites: - Antimetabolites interfere with DNA and RNA synthesis by acting as false metabolites, which are incorporated into the DNA strand or block

essential enzymes, so that DNA synthesis is prevented. Most agents are cell cycle phase specific for S phase. These agents are most effective when used against rapidly cycling cell populations and are consequently more effective against fast-growing tumours than slow-growing tumours. Major toxicities occur in the haematopoietic and gastrointestinal systems. Examples include Methotrexate, 5-Fluorourocil and Cytosine Arabinos decitabine.

Hypomethylating agents represent a class of drugs that may restore normal gene function to genes responsible for cell division and differentiation. Hypomethylating agents may function as biological response modifiers by affecting cytokine cell signaling. These agents may be identified as antimetabolites and they include 5-azacytidine and Decitabine.

3. Antitumour antibiotics: - Antitumour antibiotics (also called Anthracyclines) interfere with RNA and DNA synthesis. Most drugs are cell cycle non-specific. Major toxicities occur in the haematopoietic, gastrointestinal, cardiac and reproductive systems. Cardiac toxicity may be manifested as acute changes in the electrocardiograph (ECG) and arrhythmias. Individuals with pre-existing heart disease are most at risk. Examples include Bleomycin, Daunorubicin, and Doxorubicin.

4. Plant alkaloids: - Plant alkaloids bind to microtubule proteins during metaphase, causing mitotic arrest. The cell cannot divide and dies. This group is mainly cell cycle phase specific for M phase. Major toxicities occur in the haematopoietic, integumentary, neurologic and reproductive systems. Hypersensitivity reactions also may occur during administration of these agents.

This group contains three subgroups.

a. The vinca alkaloids e.g. vincristine and vinblastine.
b. The epipodophyllotoxins e.g. etoposide and teniposide.
c. The taxanes e.g. paclitaxel and docetaxel.

Vinca Alkaloids: Vinca alkaloids are obtained from the Madagascar periwinkle plant. They are naturally occurring or semi synthetic nitrogenous bases extracted from the pink periwinkle plant *Catharanthus roseus* G. Don. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS), but only VCR, VBL and VRL are approved for use in the United States.[4]

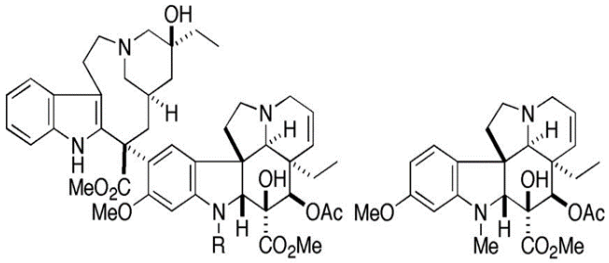


Figure 1: Vincristine & Vinblastine.

Mechanism of action of vinca alkaloid: - The main mechanisms of vinca alkaloid cytotoxicity is due to their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest. However, they can do many other biochemical activities that may or may not be related to their effects on microtubules. Many of the effects that do not include microtubule interruption happen only after treatment of cells with clinically irrelevant doses of the vinca alkaloids. Nevertheless, the vinca alkaloids and other antimicrotubule agents also have an effect on both nonmalignant and malignant cells in the nonmitotic cell cycle, because microtubules are involved in many nonmitotic functions.

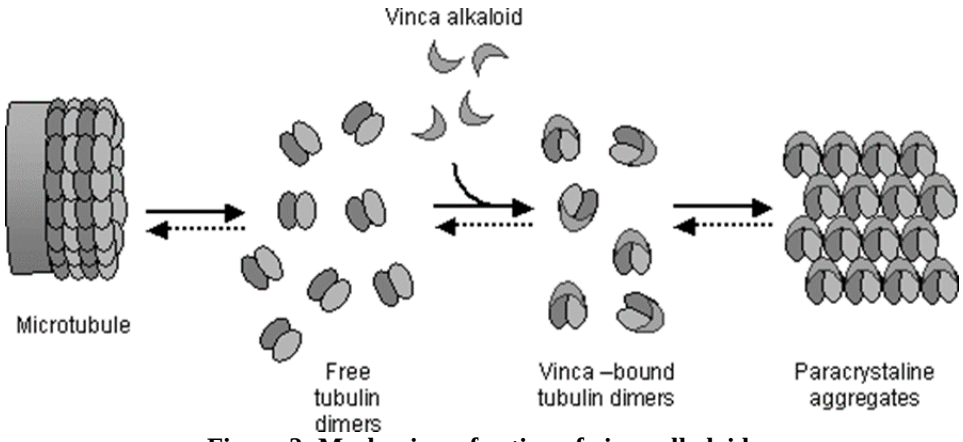


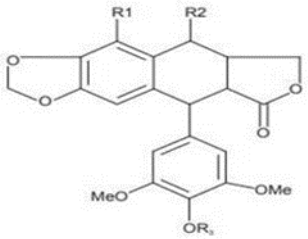
Figure 2: Mechanism of action of vinca alkaloid.

The vinca alkaloids connect to binding sites on tubulin that they are separate from those of the taxanes, colchicine, podophyllotoxin and guanosine. Binding occurs rapidly and can reverse too. Existing evidence maintains the existence of two vinca alkaloid binding sites per mole of tubulin dimer.

Semisynthetic Analogues: - The effective semisynthetic analogues that have been developed include vinorelbine and vindesine, with the most recent being vinflunine, a second-generation bifluorinated analogue of vinorelbine. These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma.[5]

Dose: - It is recommended that the Vinca alkaloids be administered by rapid intravenous injection, possibly through a running parenteral infusion. VCR is commonly administered to children weighing more than 10 kg as a bolus intravenous injection at a dose of 1.5 to 2.0 mg/m2 weekly, although 0.05 to 0.65 mg/kg weekly is commonly used in smaller children. For adults, the conventional weekly dose is 1.4 to 2.0 mg/m2. A restriction of the absolute dose of VCR to 2.0 to 2.5 mg in children and 2.0 mg in adults. VBL in combination chemotherapy regimens uses a rapid intravenous injection at a dose of 6 mg/m2 weekly. Approved dosing recommendations for weekly dosing are 2.5 and 3.7 mg/m2 for children and adults.

Uses: - These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of A variety of cancers, including leukemias, lymphomas, Advanced testicular cancer, breast and lung cancers and Kaposi's sarcoma.



Compound	R1	R2	R3
Podophyllotoxin	H	OH	CH_3
Desmethylpodophyllotoxin	H	OH	H
Desoxypodophyllotoxin	H	H	CH_3
Podophyllotoxone	H	= O	CH_3
α-Peltatin	OH	H	H
β-Peltatin	OH	H	CH_3

Figure 3: Podophyllototoxins.

Epipodophyllotoxins: In the development of the anticancer drugs, etoposide, and teniposide, as semi synthetic derivatives of epipodophyllotoxins were isolated from *Podophyllum peltatum* L. and *Podophyllum emodi* (commonly known as the American mandrake or mayapple). The structure of the major active constituent, podophyllotoxin, first isolated in 1880, was only reported in the 1950s. Clinical trials of several closely related podophyllotoxin-like lignans, however, failed due to lack of efficacy and unacceptable toxicity. Extensive research led to the development of etoposide and teniposide as clinically effective agents.

Mechanism of action: - while podophyllotoxin reversibly binds to tubulin, etoposide and teniposide inhibit topoisomerase II, inducing topoisomerase II-mediated DNA cleavage and prevent cell division. Etoposide binds and stabilizes the temporary DNA break caused by enzyme, disrupts the re-preparation of the break through which the double standard DNA passes and consequently stops DNA unwinding and replication.[6]

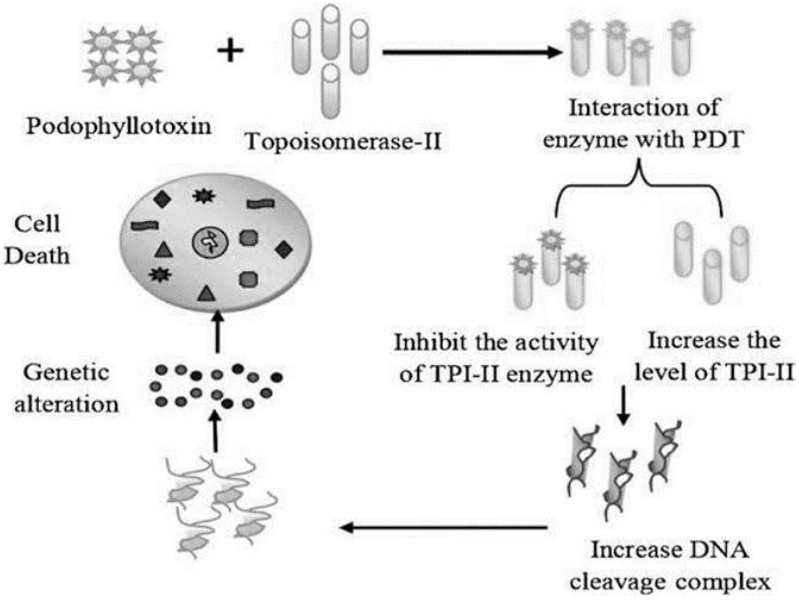


Figure 4: Mechanism of action of podophyllotoxin.

Semisynthetic analogue: - Etoposide is a semisynthetic podophyllotoxin derivative that exerts its anticancer effect through topoisomerase II inhibition. Initial studies with etoposide, which used intravenous administration on day 1 or days 1 through 3 (or 5) every 3 to 4 weeks, showed disappointing results in the treatment of BC. Later in its evaluation, schedule dependency was observed, suggesting that more prolonged exposure via an oral route may be more effective. Etoposide has approximately 50% bioavailability orally. In a Phase II study in previously treated MBC patients, an objective RR was observed in 15 of 43 patients (35%) with a schedule of 50 mg/m2 daily for 21 days every 4 weeks. Oral etoposide is generally well tolerated, with myelosuppression, alopecia, and mucositis as the main adverse effects.

Dose: - Podophyllum should not be used for self-treatment. Covering too much skin with podophyllum or applying it to broken skin increases the chance of getting poisoned. It's safer to use podophyllotoxin, which is an FDA-approved drug. A 0.5% podophyllotoxin gel is applied twice daily for three days in a row and repeated for two to four cycles. Podophyllotoxin is a chemical taken from podophyllum. Podophyllotoxin (podofilox, Condylox) is an FDA-approved drug. Podophyllotoxin might be more effective than podophyllum and is less toxic.

Uses: - For treatment, etoposide and teniposide are used for lymphomas, and bronchial and testicular cancers. The history of the development of these agents and some related analogues under clinical investigation has been reviewed.

Taxanes: A more recent addition to the armamentarium of plant derived chemotherapeutic agents are the taxanes, *Taxus baccata* and *Taxus brevifolia* are members of the yew family (Taxaceae). *T. baccata* is commonly known as the English yew. *T. brevifolia* is most commonly known as the Pacific Yew.[7]

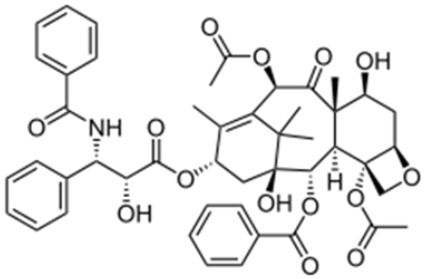


Figure-5: Taxol.

Mechanism of action: - *In-vitro*, paclitaxel enhances the polymerization of tubulin to stable microtubules and also interacts directly with microtubules, stabilizing them against depolymerization by cold and calcium, which readily depolymerize normal microtubules. The fact that the drug has a specific binding site on the microtubule polymer makes it unique among chemotherapeutic agents, and the ability of paclitaxel to polymerize tubulin in the absence of cofactors like guanosine triphosphate and microtubule-associated proteins is unusual. When paclitaxel and microtubule protein are irradiated with ultraviolet light, the drug preferentially binds covalently to the beta-subunit of tubulin. Paclitaxel and Other taxanes promote the polymerization of tubulin heterodimers to microtubules, suppressing dynamic changes in microtubules resulting in mitotic arrest.

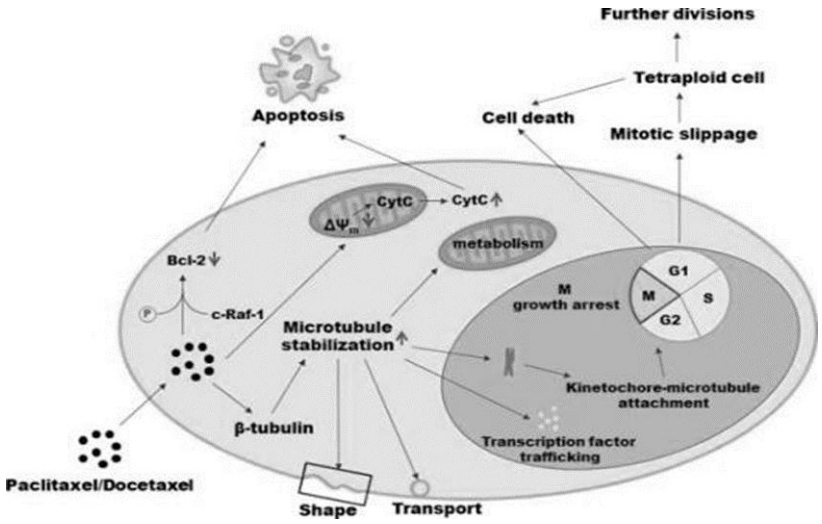


Figure-6: Mechanism of action.

Semisynthetic analogue:- Currently, the two most clinically effective drugs of this class are paclitaxel and docetaxel a semisynthetic analogue synthesized From DAB (10- deacetylbaccatin III) isolated from the Leaves of the European yew, *Taxus baccata*. DAB has also been semisynthetically converted to paclitaxel, thereby providing a sustainable source of the drug. It is interesting to note that the leaves of *T. Baccata* are used in the traditional Asiatic Indian (ayurvedic) medicine system, with one reported use being in the treatment of 'cancer.

Dose: - Paclitaxel Injection administered intravenously over 3 hours at a dose of 175 mg/m² followed by

cisplatin at a dose of 75 mg/m²; For the adjuvant treatment of node-positive breast cancer, the recommended regimen is paclitaxel injection, at a dose of 175 mg/m² intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy.[8]

Uses: - Paclitaxel is used in the treatment of breast, ovarian and non-small cell lung cancer (NSCLC), and has also shown efficacy against Kaposi's sarcoma, while docetaxel is primarily used in the treatment of breast cancer and NSCLC. A comprehensive review of the taxanes as well as ongoing research into the development of improved analogues.

Camptothecin: Camptothecins (CPTs) were isolated from the Chinese ornamental tree *Camptotheca acuminata Decne* (Family Nyssaceae).

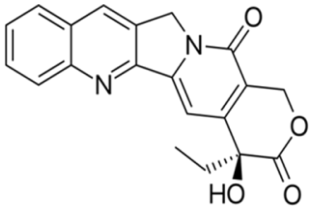


Figure-7: Camptothecin.

Mechanism of action: - The mechanism of action is through binding to the topoisomerase I-DNA binary complex resulting in a stable ternary complex, thereby preventing DNA religation and causing DNA damage, which results in apoptosis. Clinical trials of the water-soluble sodium salt in the 1970s, however, were terminated due to severe bladder toxicity.

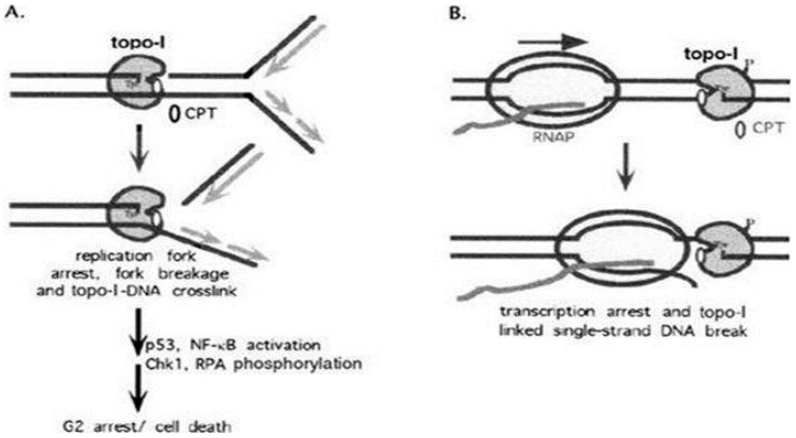


Figure-8: Mechanism of action.

Semisynthetic analogue: - Irenotecan (CPT-11) is another semisynthetic analogue of camptothecin with improved water solubility, owing to its basic side chain. Irenotecan serves as a prodrug and is hydrolyzed in vivo to its active metabolite, 7-ethyl-10-hydroxycamptothecin. Aminocamptothecin is another camptothecin derivative undergoing clinical trials. Problems associated with the water solubility of 9-aminocamptothecin have been overcome by employing an infusion formulation containing polyethylene glycol and phosphoric acid.[9]

Dose: - A single subcutaneous injection of CPT-SSM-VIP (0.1 mg/kg) administered to CIA mice mitigated joint inflammation for at least 32 days thereafter without systemic toxicity. CPT alone needed at least 10-fold higher dose to achieve the same effect, albeit with some vacuolization in liver histology.

Uses: - The camptothecin topoisomerase I-targeting agents are new class of antitumor drugs with demonstrated clinical activity in human malignancies, such as colorectal cancer and ovarian cancer. Currently, irinotecan and topotecan are the most widely used camptothecin analogs in clinical use and clinical trials are ongoing to better characterize their spectra of clinical activity, to determine their optimal schedules of administration and to define their use in combination with other chemotherapeutic agents. Other potential clinical applications include the use of camptothecin derivatives as radiation sensitizers or as antiviral agents. The successful development of the camptothecins as antitumor agents highlights the importance of topoisomerase I as a target for cancer chemotherapy.

Combretastatins: The combretastatins are a family of stilbenes originally isolated from the root bark. *Combretum caffrum*, also known as the Cape bushwillow in southern Africa.

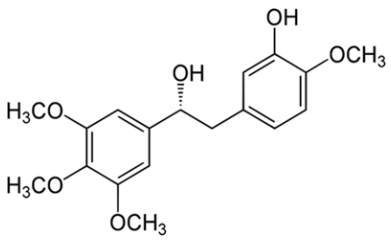


Figure-9: Combretastatin.

Mechanism of action: - binding to colchicine domain of microtubules, which affects the cytoskeleton functionality of immature endothelial cells. At the same time, combretastatin directly induce cell death via apoptosis and/or mitotic catastrophe pathways. The combination of both elements makes combretastatin an anticancer compound of high efficiency.

Semisynthetic analogue: - Tubulin protein is a major target for anticancer drug discovery. As a result, antimitotic agents constitute an important class of the current anticancer drugs. Hundreds of tubulin inhibitors, naturally occurring, semisynthetic or synthetic, have been reported. Among these, combretastatin A-4 (CA-4), isolated from a South African tree Combretum caffrum, is one of the most potent antimitotic agents. CA-4 shows strong cytotoxicity against a variety of cancer cells, including multi-drug resistant cancer cell lines. It has also been demonstrated to exert highly selective effects in proliferating endothelial cells. CA-4 disodium phosphate (CA4DP), a water-soluble prodrug of CA-4, shows potent antivascular and antitumor effects in a wide variety of preclinical tumor models.[10]

Dose: - The drug was delivered by a 10-minute weekly infusion for 3 weeks followed by a week gap, with interpatient dose escalation. Dose escalation was accomplished by doubling until grade 2 toxicity was seen. The starting dose was 5 mg/m^2.

Uses: - It is a water-soluble prodrug that the body can rapidly metabolize to combretastatin A4, which exhibits anti-tumor properties. In addition, in vitro and in vivo studies on combretastatin have determined that these compounds also have antioxidant, anti- inflammatory and antimicrobial effects.

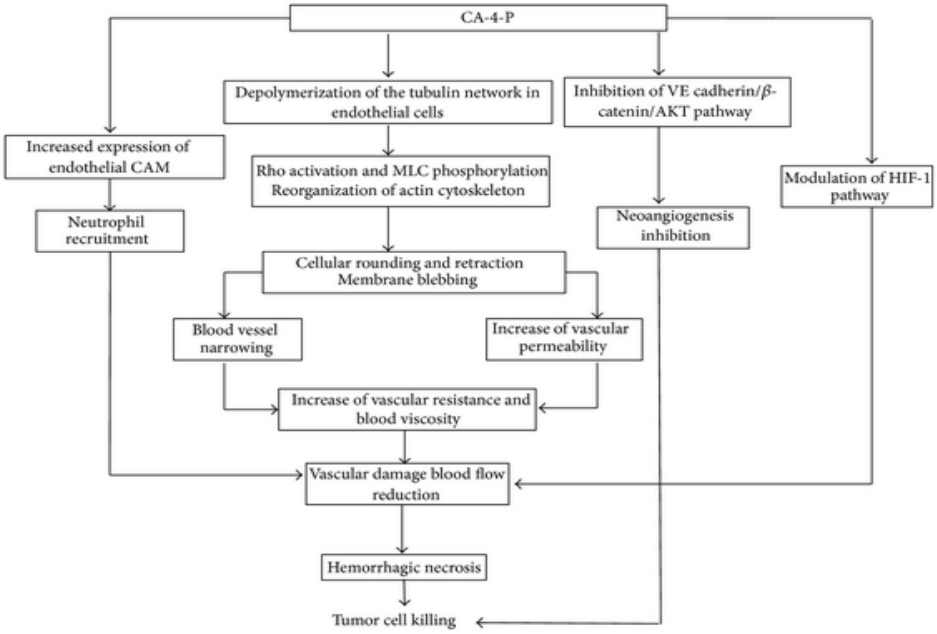


Figure-10: Mechanism of action.

Antineoplastic agents Derived from Marine Organisms: - Despite covering roughly 70% of the planet, less than 5% of the deep sea has been pharmacologically explored in any way, and less than 0.01% of the deep-sea floor has been sampled in detail. A significant number of marine-derived antitumor agents showing potent growth inhibition of human tumor cells in vitro and, in a number of cases, in in vivo murine models and in humans have been isolated, but although many agents have entered clinical trials in cancer, to date only four have been approved for use in humans. These agents are as followings.

Cytarabine and Nucleoside Analogues: It can be argued that the discovery by Bergmann and Burke in the early 1950s of the arabinose-containing bioactive nucleosides, spongothymidine and spongouridine, from the Caribbean sponge *Tethya crypta* sparked the exploration of the marine environment as a source of novel bioactive compounds that could serve as leads to potential drugs. This discovery led to the identification and development of analogues such as cytarabine (AraC) as a potent antileukemic agent, and the antiviral agent, AraA (adenine arabinoside).

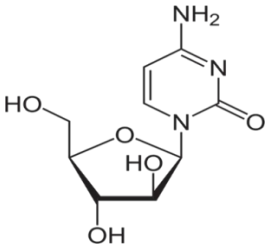


Figure-11: Cytarabine.

Mechanism of action: - Cytarabine is a pyrimidine analogue and is also known as arabinosylcytosine (ARA-C). It is converted into the triphosphate form within the cell and competes with cytidine to incorporate itself in the DNA. The sugar moiety of cytarabine hinders the rotation of the molecule within the DNA. The DNA replication ceases, specifically during the S phase of the cell cycle, which makes it a specific drug for rapidly dividing cells, such as those seen in cancer. DNA replication and repair also halt due to the inhibition of DNA polymerase by cytarabine. This drug must act for a time that is equivalent to one cell cycle to inhibit the replication of tumor cells effectively. Hence the bolus dose of cytarabine is given every 8 to 12 hours to maintain optimum intracellular levels.[11]

Semisynthetic analogue: - Cytosine arabinoside (Ara-C), or cytarabine, acts as an analog to deoxycytidine and is phosphorylated in cells to generate arabinosylcytosine triphosphate (ara-CTP), which acts as a competitive inhibitor of DNA polymerase α. Ara-CTP is also incorporated into DNA, which correlates with cytotoxicity and thus presumably is the primary mechanism of action. Once incorporated into DNA, it cannot be excised and inhibits both the function of the DNA template and subsequent synthesis.

Dose: - Cytarabine may be given as an infusion into the vein (intravenous or IV). 100 mg/m2 daily for 7 days via continuous IV infusion or cytarabine 100 mg/m2 IV every 12 hours for 7 days; give in combination with other anticancer drugs.

Uses: - Cytarabine is used alone or with other chemotherapy drugs to treat certain types of leukemia (cancer of the white blood cells), including acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and chronic myelogenous leukemia (CML).

Trabectedin: Trabectedin is an alkylating agent approved for the treatment of unresectable or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma).

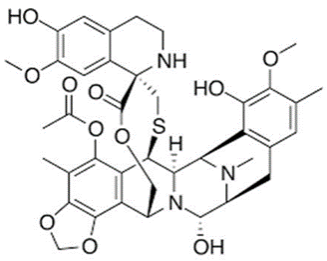


Figure-12: Trabectedin.

It was approved for use in Europe for the treatment of advanced soft-tissue sarcoma and has been granted orphan drug status for the treatment of soft-tissue sarcoma and ovarian cancer by the FDA and the EMA. It was the first 'unmodified' marine-derived natural product to be approved for the treatment of cancer, and it is undergoing clinical trials for the treatment of breast, prostate, and pediatric sarcomas. Antineoplastic agents derived from bacteria and fungi: - Antitumor antibiotics are amongst the most important of the cancer chemotherapeutic agents. These include members of the actinomycin, ansamycin, anthracycline, bleomycin, epothilone, and staurosporin classes. Except for the epothilones, which are metabolites of the myxobacterium *Sorangium cellulosum*, metabolites of the other classes were isolated from various Streptomyces species. Some recent advances in the development of other microbial-derived anticancer agents are given in the following sections.

Rapamycins: The discovery of rapamycin a 31-membered macrocyclic antibiotic produced by the fermentation of a strain of *Streptomyces hygroscopicus* isolated from soil samples in Rapa Nui (Easter Island) was first reported in 1975.

Chemical modifications have yielded two clinically approved anticancer drugs. Everolimus was initially approved as an immunosuppressive agent in 2004, but approval was granted for the treatment of kidney, brain, pancreatic, and breast cancers in 2009, 2010, 2011, and 2012, respectively. It is also currently in, or has recently completed, phase III trials for treating diffuse large B-cell lymphoma, liver, and stomach cancers. Temsirolimus proved as a treatment for renal carcinoma in 2007 and is currently in phase II trials for the treatment of various carcinomas. Another rapamycin derivative showing promise in the treatment of cancer is ridaforolimus, which has recently completed a phase III trial for the treatment of soft-tissue carcinoma and bone cancer.[12]

Carfilzomib: Carfilzomib a synthetic analogue of epoxomicin, a peptide α′, β′-epoxyketone isolated from an actinomycete strain, is a proteasome inhibitor which binds through a covalent, selective, and stereospecific linkage to the chymotryptic subunit (20S) of the proteasome. It was approved by the FDA in 2012 for the treatment of patients with relapsed and refractory multiple myeloma who had received prior treatment with bortezomib, thalidomide, or lenalidomide. Phase II trials are ongoing for the treatment of a variety of other cancers.

Maytansinoids: Maytansine a novel macrocyclic compound was isolated in extremely low yield in the early 1960s from the Ethiopian plant, *Maytenus serrata* (Hochst. ex A. Rich.) Wilczek and was shown to exhibit very potent in vitro an antitumor activity. Thus, further development was pursued, but despite the promising activity observed in preclinical animal testing, insignificant efficacy was observed in human clinical trials, and studies were terminated in the early 1980s. Due to its structural similarity to the 'ansa' antibiotics, such as the rifamycins, natural product chemists had wondered if maytansine was of microbial origin. In 1977, the isolation of the closely related ansamitocins

from the bacterium *Actinosynnema pretiosum* strengthened this speculation, and a report by members of the Leistner group, who identified a very closely related Actinosynnema sp. in the microbial root system of plants producing maytansine, coupled to the complete absence of a required AHBA synthase gene in plant cell cultures of the nominal host plant, provided further circumstantial evidence for the bacterial source of the maytansinoids. The ansamitocins provided a ready and sustainable source of maytansinoids, and the derivatives DM1 and DM4 have been prepared from appropriate ansamitocins.

Developments Towards Newer Anticancer Agents: - In the early development of modern medicine, biologically active compounds from higher plants have played a vital role in providing medicines to combat pain and diseases. For example, the organic monographs of British Pharmacopoeia of 1932 had more than 70% plant-derived products. However, with the advent of synthetic medicinal chemistry, the role of plant derived therapeutic agents significantly declined (mostly) in the economically developed nations. The synthetic drugs are more toxic to animal body. Besides curing cancer, they harm the normal cells of the body and are producing severe side effects that are not only long living but may pose threat to patient's life.[13]

Ganoderma lucidum, commonly referred to as Lingzhi in Japan or Reishi in China, has been used in Asia for health promotion for centuries. It is considered to be a natural medicine that promotes longevity and maintains the vitality of human beings. Its beneficial clinical effects in patients with hepatitis, hyperglycemia, chronic bronchitis, cancer, muscular dystrophy, arteriosclerosis, hypertension, hypercholesterolemia, and leukopenia have been confirmed in pharmacologic studies in recent years. The fruiting bodies, mycelia, and spores have recently received more and more attention not only as home remedies but also as new drug sources. The anti-cancer effects of *G. lucidum* have been demonstrated in both *in-vitro* and *in-vivo* studies. In addition, the observed anti-cancer activities of Ganoderma have prompted its usage by cancer patients alongside chemotherapy. The usefulness of Ganoderma in benign prostatic hyperplasia has already been reported in rat models.

Sphaeranthus indicus (Compositae) is an herb found mostly in southern India. It is bitter stomachic, stimulant, alterative, pectoral, demulcent, and external emollient. The herb is an ingredient ofcertain proprietary marketed preparation in India, namely, "Prostabliss" used for the management of benign prostatic hyperplasia. Nahata et al., (2013) screened S. indicus, Ganoderma lucidum and Urtica dioica for their cytotoxicity against human cancer cell lines and found S. indicus to be the most effective in inhibiting the proliferation of prostate cancer cell lines, that is, PC-3 and DU-145. The petroleum ether, ethanol and aqueous extracts of the test drugs were screened for their in vitro cytotoxicity. S. indicus proved to be the best in these studies and its petroleum ether extract exhibited inhibitory activity against most of the human cancer cell lines, namely, lung (A549), prostate (PC-3 andDU-145), colon (Colo-205), neuroblastoma (IMR-32), and breast cancer (MCF-7). It was concluded that *S. indicus* induces apoptosis through mitochondrial-dependent pathway in HL-60 Cells and exerts cytotoxic potential on several human cancer cell lines. Sphaeranthus indicus and *Urtica dioica* have already been reported for their usefulness in benign prostatic hyperplasia.

The pomegranate tree, *Punica granatum*, especially its fruit, possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. The tree/fruit can be divided into several anatomical compartments: seed, juice, peel, leaf, flower, bark and roots, each of which has interesting pharmacologic activity. Juice and peels, for example, possess potent antioxidant properties, while juice, peel and oil are all weakly estrogenic and heuristically of interest for the treatment of menopausal symptoms and sequelae. The use of juice, peel and oil has also been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis.[14]

Betulinic acid, a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from Betula species (Betulaceae). Pisha et al., (1995) extracted *Ziziphus mauritiana* Lam. (Rhamnaceae) collected in Zimbabwe. The ethyl acetate-soluble extract displayed selective cytotoxicity against human melanoma cells (MEL-2). Betulinic acid was then found to be active *in-vivo* using athymic mice carrying human melanomas, with little toxicity. Further biological studies indicated that betulinic acid works by induction of apoptosis. Pre-clinical development towards a topical formulation is also ongoing.

The Chinese herbal medicine *Radix sophorae* is widely applied as an anti- carcinogenic/anti-metastatic agent against liver cancer. Cheung et al., (2007) showed that Leachianone A, isolated from *Radix sophorae*, possessed a profound cytotoxic activity against human hepatoma cell line HepG2 in vitro, with an IC50 value of 3.4 mg/ml post-48-h treatment. Its mechanism of action involved both extrinsic and intrinsic pathways of apoptosis. Its anti-tumor effect was further demonstrating *in-vivo* 17-54% reduction of tumor size in HepG2-bearing nude mice, in which no toxicity to the heart and liver tissues was observed. In conclusion, this is the first report describing the isolation of Leachianone A from Radix sophorae and the molecular mechanism of its anti-proliferative effect on HepG2 cells.

Turmeric has been shown to possess variety of pharmacological properties such as anti-inflammatory, anti-carcinogenic and anti-oxidant by different workers. Yasmin et al., (1998) have reported that turmeric also

activates the lymphocytes and induces apoptosis of tumor cells. Spectrofluorimetric determination can now be carried out for curcumin in any formulation or drug mixtures.

The antitumor activity of the methanolic extract of *Glinus lotoides* has been evaluated against Dalton's ascitic lymphoma (DAL) in Swiss albino mice. A significant enhancement of mean survival time of tumor bearing mice and peritoneal cell count in normal mice was observed with respect to the control group.

5. Hormonal agents: - Hormonal agents alter the internal / extracellular environment. Most agents are cell cycle phase non-specific. Breast, thyroid, prostate and uterine cancers are examples of tumours that are sensitive to hormonal manipulation. With these diseases, the action of hormones or hormone antagonists depends on the presence of hormone receptors in the tumours themselves (i.e. oestrogen receptors in breast cancers). There are individual classifications of hormonal agents.

1. Adrenocorticoids, e.g. prednisone
2. Androgens, e.g. testosterone propionate
3. Oestrogens, e.g. diethylstilbestrol
4. Selective oestrogen receptor modulators, e.g. tamoxifen citrate
5. Selective aromatase inhibitors, e.g. anastrozole
6. Progesterones, e.g. megestrol acetate
7. Antitestosterone, e.g. flutamide

6. Miscellaneous agents: - Miscellaneous agents differ from any of the major classes of cytotoxic agents. Common miscellaneous agents are asparaginase and hydroxyurea. Topoisomerase inhibitors prevent re-aligning of DNA strands and maintain single-strand breaks. Major toxicities occur in the haematopoietic and gastrointestinal systems. Examples include irinotecan and topotecan. Major toxicities occur in the gastrointestinal, sexual / reproductive systems and mood and sleep pattern changes.[15]

Concluding Remarks and Future Prospects: - It is clear that there is a scope for continuous and multiple opportunities for the development of novel analogues, prodrugs, and methods of administration of agents from well-established drug classes, such as Camptothecin (CPTs), nucleosides, taxanes, and vinca alkaloids, and that in many instances these can lead to the development of products having superior clinical efficacy and decreased toxicity. The conjugation of potent cytotoxic natural products to monoclonal antibodies specifically targeting epitopes on tumors of interest offers another promising approach to developing effective chemotherapeutic anticancer agents. In addition, new lead compounds are being discovered from natural sources, and these are providing new avenues for the development of novel and effective chemotherapeutic agents.

Every year, cancer takes the lifetime of various individuals. Varied therapies area unit out there for the cancer treatment however they need many limitations like excretory organ injury, gastro- intestinal disorder, etc., because of that another answer to the current drawback is needed. Plant derived compounds possessing anti-cancerous activities have received vast quantity of scientific attention. They play very important role within the cancer bar and treatment. Pharmaceutical analysis has been worn out countries like European nation, USA, Japan, France and China to enhance the standard of flavouring drugs for the cancer treatment. Plants area unit the major supply of secondary metabolites and a vital supply of pharmaceutical medicine. Herbal drug treatment is a perfect selection because it is relatively cheaper and will be extremely recommended to the poor and rural individuals for the effective treatment of cancer. Anticancer agents discovered from meditative plants have competed a vital role in cancer treatment. It is documented that meditative herbs have made antitumor potential because of their immune- modulatory and inhibitor properties, and on the forefront whenever we have a tendency to mention anticancer remedies, they're a major supply of artificial and/or flavouring origin. Bioactive compounds considerably influenced the cancer analysis on varied aspects. Secondary metabolites from medicinal plants inhibits the DNA injury, arrest the cell cycle, inhibits the tumour cell growth and induce cell death so prevents the cancer. Researchers should pay attention to the scientific rigor of studies of flavouring medicine within the future to enhance the standing. So, In this context selected plants are being explored for their biological activity, however more additional efforts are to be given to explore potent antitumor plants from nature to save lots of human's life across the globe from cancer.

REFERENCES

1. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. SEER.http://seer.cancer.gov/statfacts/html/all.html (accessed April 30, 2015).
2. Verma M, Singh SK, Bhushan S, SharmaVK, DattP, et al., (2008) In vitro cytotoxic potential of Polyalthia longifolia on human cancer cell lines and induction of apoptosis through mitochondrial-dependent pathway in HL-60 cells. Chem Biol Interact, 171(1): 45-56.
3. Hong WK, Sporn MB: Recent advances in chemoprevention of cancer. Science, 1997; 278: 1073–1077.
4. Shi M, Cai Q, Yao L, Mao Y, Ming Y, et al., (2006) Antiproliferation and apoptosis induced by curcumin in human ovarian cancer cells. Cell Biol Int, 30(3): 221-6.
5. Newman DJ, Cragg GM: Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod, 2012; 75: 311-335.
6. Hartwell JL (1971) Plants used against cancer- A survey. Lloydia, 34(4): 204-55.

7. Cragg GM, Newman DJ: Nature: a vital source of leads for anticancer drug development. Phytochem Rev, 2009; 8: 313-331.
8. Hande KR (1998) Etopside: four decades of development of a topoisomerase II inhibitor. Eur J Cancer, 34(10): 1514-21.
9. Cragg GM, Grothaus PG, Newman DJ: Impact of natural products on developing new anti-cancer agents. Chem Rev, 2009; 109: 3012–3043.
10. Chabner BA, Lango DL (2001) Topoisomerase II inhibitors: the epipodophyllotoxins, m–AMSA and the ellipticine derivatives. Cancer Chemotheraphy and Biotherapy: Principles and Practice. 3rd (Edn), Lippoincott Williams and Wilkins, Philadelphia.
11. Hartwell JL: Plants Used against Cancer. Lawrence, Quarterman, 1982.
12. Dougherty, L. and C. Bailey, Chemotherapy, in Cancer nursing: care in context, J. Corner and C. Bailey, Editors. 2009, Blackwell Publishing Ltd: Malden MA.
13. Otto, S.E., Chemotherapy, in Oncology nursing, M.E. Langhorne, J.S. Fulton, and S.E. Otto, Editors. 2007, Elsevier Mosby.: St Louis.
14. Polovich, M., J. Whitford, and N. Olsen, eds. Chemotherapy and biotherapy guidelines and recommendations for practice. 3rd ed. 2009, Oncology Nursing Society: Philadelphia.
15. Barton-Burke, M. and G. Wilkes, Cancer chemotherapy and cell cycle kinetics, in Cancer therapies, M. Barton-Burke and G.M. Wilkes, Editors. 2006, Jones & Bartlett Publishers: Massachusetts.