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A REVIEW ON: THE ROLE OF NATURAL PRODUCTS IN ANTICANCER DRUG DEVELOPMENT

[1]Akanksha Balaso Kumbhar, [2]*Vijaykumar S. Wakale

[1]Student, Samarth Institute of Pharmacy, Belhe, Pune, Maharashtra, India.
[2]Professor Samarth Institute of Pharmacy, Belhe, Pune Maharashtra, India.

***Corresponding Author: Vijaykumar S. Wakale**

Professor Samarth Institute of Pharmacy, Belhe, Pune Maharashtra, India.

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ABSTRACT

Natural products have historically been a rich source for cancer treatments, as cancer is expected to be one of the leading causes of death in this century. Nonetheless, there remains an ongoing necessity for the advancement of new anticancer medications, drug combinations, and chemotherapy approaches through systematic and scientific investigation of the vast array of synthetic, biological, and natural products. A variety of compounds have been created from natural products through structural modifications or by utilizing naturally occurring substances as foundational elements in the synthesis of these compounds for a range of applications across various domains, including biology, medicine, and engineering. Numerous contemporary and expensive therapies have been implemented to fight cancer and reduce its fatality, yet the outcomes are not significantly groundbreaking. Natural compounds, which are a vital source of novel therapeutic medicines, are now being explored as potential cytotoxic agents. They have demonstrated favorable trends in preclinical studies and have inspired a variety of innovative strategies to defeat cancer and accelerate clinical research. The significance of natural products for drug discovery is increasing due to their extensive molecular diversity and unique biofunctional characteristics. Additionally, natural compounds can offer enhanced effectiveness and safety owing to their distinct molecular attributes. Naturally occurring compounds from plants have served as a significant source of various anti-cancer medications used in clinical settings. Among these are vinblastine and vincristine, as well as the camptothecin derivatives, which include topotecan and irinotecan. Additionally, etoposide, which is derived from epipodophyllotoxin, and paclitaxel (taxol®) are also noteworthy.

KEYWORDS: Anticancer, Plant-Based Anti-Cancer Agent, Natural product.

INTRODUCTION

Natural products have played a significant role in the development of anticancer drugs. Many commonly used cancer treatments come from natural sources, including irinotecan, vincristine, etoposide, and paclitaxel, which are derived from plants, as well as actinomycin D and mitomycin C from bacteria, and marine-derived bleomycin. These compounds remain essential in cancer treatment and are expected to continue being important in the coming years. Among them, camptothecin and taxol stand out as the most successful examples. Both were discovered between the 1950s and 1960s as part of a program led by the National Cancer Institute (NCI) aimed at exploring the potential of natural products for therapeutic use.[1,2] Except for minerals and synthetic substances, all natural elements are composed of organic compounds derived from natural sources. These compounds can be of pre-biotic origin or come from microbial, plant, or animal sources. Examples of such compounds include polyketides, terpenoids, amino acids, proteins, carbohydrates, lipids, nucleic acid bases, RNA, and DNA. The study of natural products is rooted in humanity's innate curiosity about sensory experiences such as smell, taste, color, and the potential for healing. Nature has served as a source of medical treatments for thousands of years, and even in the present day, plant-based systems remain crucial for primary healthcare, benefiting approximately 80% of the global population.[3-5]

The list of synthetic anti-cancer compounds derived from plant sources includes Camptothecin and its derivatives, such as Belotecan (Camptobells); Paclitaxel (Taxols) and its related compounds like Docetaxel (Taxoteres), Vinblastine (Velbans); Podophyllotoxin and its derivatives, Etoposide (Etopophoss) and Teniposide (Vumons); Vincristine (Oncovins) and its related compounds, Vindesine (Eldisines), Cabazitaxel (Jevtanas), Irinotecan (Camptosars), Topotecan (Hycamtins), and Vinorelbine (Navelbines).[6-8]

Soil-derived bacteria are also remarkable sources of anti-cancer drugs, including anthracyclines like Doxorubicin (Doxils, Adriamycins), nonribosomal peptides such as Dactinomycin (Cosmegens), Daunorubicin (Cerubidines), Epirubicin (Ellences), and the glycopeptide bleomycin (Blenoxanes).[9-10]

Plant-Based Anti-Cancer Agents

The vinca alkaloids

The first agents to be used in clinical settings were the socalled vinca alkaloids, specifically vinblastine (VLB) and vincristine (VCR).

These compounds were extracted from the Madagascar periwinkle, scientifically known as Catharanthus roseus G. Don, which belongs to the Apocynaceae family. This plant has been utilized by different cultures for the treatment of diabetes. [11] A thorough search for the active component in Catharanthus roseus G. Don, which was previously known as Vinca rosea Linn from the Apocyanaceae family, led to the identification of its ability to fight cancer. This discovery was made by research teams in Canada and the United States. Subsequent studies in this field focused on isolating and determining the structure of the dimeric compound, Vinblastine 13, which was found to be highly effective.[12] Vincristine 14, Leurosine 15, Leurosidine 16[12,13] These compounds have been developed as commercial drugs. They also inhibit microtubule formation by attaching to tubulin at a different site compared to Colchicine. Following studies have demonstrated.[13, 14] Cartharanthus roseus contains more than seventy-five alkaloids, and while some of these compounds have anti-cancer properties, their effectiveness is not as strong as other known treatments. Vinca alkaloids, such as vincristine and vinblastine, attach to a specific part of tubulin heterodimers known as the vincu-binding site. This binding can either interfere with the function of microtubules or stop the cell cycle at the metaphase stage, which can be harmful to cancer cells. Over time, several semi-synthetic versions of these alkaloids have been developed and made available for use. These modified compounds are often used on their own or in combination with other plant-based chemicals to treat various types of cancer.[15,16]

Table 1: Natural anti-cancer drugs and synthetic analogs.[17]

Sr.No.	Antitumor agent	Natural Source/ derivative	Applications and targets	Mechanism of Action (MOA)
1.	Vinblastine (VBS)	Vinca rosea L.	Breast cancer, testicular cancer, neuroblastoma, Hodgkin's and non-Hodgkins lymphoma, mycosis fungoides, histiocytosis, and Kaposi's sarcoma	The mechanism of action (MOA) of vinblastine is mainly attributed to its ability to inhibit mitosis during the metaphase stage. This occurs through its interaction with tubulin, a protein essential for microtubule formation. Vinblastine attaches to the microtubular proteins in the mitotic spindle, causing the microtubules to become rigid and crystalline. This structural change results in the arrest of the cell during mitosis or leads to cell death.[18,19]
2.	Vincristine (VCS)	Vinca rosea L.	Leukemia, malignant lymphoma, Hodgkin's disease, acute erythraemia, and acute panmyelosis	Like other vinca alkaloids, Vincristine is reported to be a primary inhibitor of mitosis at metaphase via its interaction with tubulin and causes apoptotic cell death.[20]
3.	Vindesine (VDS)	Vincristine analog	Acute lymphocytic leukemia	Vindesine binds to the proteins in the mitotic spindle that make up microtubules, causing these structures to form crystals. This process stops the cell from finishing mitosis, which can lead to the death of the cell.[21]
4.	Vinorelbine (VRB)	Vincristine analog	Metastatic non-small cell lung carcinoma	Vinorelbine primarily targets tubulin and microtubules. At higher concentrations, it promotes the breakdown of microtubules and leads to the destruction of the mitotic spindle, whereas at lower concentrations, it inhibits the progression of cells through mitosis. Vinorelbine attaches to the β-tubulin subunits near the end of microtubules where the Vinca-

				binding site is located. The quick and reversible interaction of Vinorelbine with soluble tubulin causes a structural change in tubulin, which enhances its ability to bind to itself. This process is crucial for the dynamics and stability of microtubules.[22]

Camptothecin

Camptothecin, which was first identified from the wood and bark of the plant Camptotheca acuminata, showed potential as a cancer treatment in the early 1960s. However, its use as an anticancer drug remained limited for about two decades until scientists discovered how it works to fight cancer.[23-24] Camptothecin can specifically bind to topoisomerase I, which is an important enzyme involved in DNA replication and transcription. When this enzyme is trapped by camptothecin, it forms complexes with DNA. These complexes can create significant stress in the genome when they interact with the replication process or transcription machinery, ultimately resulting in cell death.[25] This special way of working sparked renewed interest in creating camptothecin derivatives, with the goal of improving their solubility, reducing their harmful effects, and maintaining their cancer-fighting properties. In the mid-1990s, two camptothecin derivatives, topotecan and irinotecan, were approved by the Food and Drug Administration (FDA) for the treatment of different cancer types, including ovarian, lung, breast, and colon cancers. Also, 10-hydroxycamptothecin, which has lower toxicity than camptothecin, has been used in China since the 1970s to treat hepatoma, colon cancer, and bladder cancer.

The development of taxol (paclitaxel) follows a similar path, although it faced greater challenges, making it a classic example of how natural products progress from discovery to clinical use.

The first major challenge was the limited availability of the compound, a common issue with natural products. Initially, taxol was found in the bark of Taxus brevifolia, which is a limited resource and only produces small amounts of the compound. This problem was addressed through a commercially viable semi-synthetic method that began with 10-DAB, a compound that can be sourced from a renewable plant. The next difficulty was understanding its complex chemical structure, which was solved in 1971 using techniques such as mass spectrometry, X-ray crystallography, and NMR spectroscopy—approaches that are now routine but were still emerging at the time. The mechanism of action of taxol was identified in 1979, revealing that it binds to microtubules and disrupts their normal function, leading to the death of cancer cells during mitosis. The final challenge was poor solubility, which was overcome by a special formulation containing castor oil called Cremophor EL, eventually enabling taxol to enter clinical trials. In December 1992, more than twenty years after its initial discovery and structural determination, the FDA approved taxol for the treatment of resistant ovarian cancer.[26,27,28,29]

Even today, the impact of camptothecin and taxol remains strong. Further research has led to the development of several new camptothecin derivatives that show better drug performance. Some of these derivatives have already entered clinical trials. One example is chimmitecan, a camptothecin derivative created by scientists at the Shanghai Institute of Materia Medica, part of the Chinese Academy of Sciences. It is currently in phase II trials in China.[25,30] By using an albumin-bound nanoparticle (nab) technology, paclitaxel was able to avoid the significant toxic effects associated with traditional formulations and accumulate more effectively in tumor tissues.[31,32] Nab-paclitaxel has been approved in 2005 for the treatment of metastatic breast cancer, followed by indications in pancreatic cancer and non-small cell lung cancer.

Table 1: Natural anti-cancer drugs and synthetic analogs.[17]

SrNo.	Antitumor agent	Natural Source/ derivative	Applications and targets	Mechanism of Action (MOA)
1.	Camptothecin (CPT)	Camptotheca acuminata Decne	Nuclear enzyme DNA topoisomerase type I inhibitor	CPT binds to the topoisomerase I (topo-I) and DNA binary complex resulting in a stable ternary complex, thereby stopping DNA relegation and causing DNA damage, which results in apoptosis. CPT's primary mechanism of cell killing is S-phase-specific killing by hard collisions between advancing replication forks and topo-I cleavable complexes. Collisions with the transcription machinery have also been shown to trigger the formation of long-lived covalent topo-I DNA complexes, which contribute to CPT cytotoxicity.[33]

2.	Belotecan (BLT)	Camptothecin analog	Epithelial Ovarian Cancer	BLT is an analog of CPT and shows similar MOA to CPT. BLT binds and inhibits the topo I activity, stabilizing the cleavable complex of topo I–DNA, which inhibits the religation of single-stranded DNA (ssDNA) disruptions caused by topo I. Lethal double-stranded DNA (dsDNA) interruptions occur when the DNA replication machinery encounters the topo I–DNA complex, DNA replication is disturbed, and the tumor cell undergoes apoptosis.[34]
3.	Topotecan (TPT)	Camptothecin analog	Ovarian cancer	The MOA of TPT acts by making a stable covalent complex with the DNA/topo I aggregate. This socalled cleavable complex is responsible for the cytotoxic properties of topotecan. This process leads to breaks in the DNA strand resulting in apoptosis and cell death.[35]
4.	Irinotecan (INT)	Camptothecin analog	Antineoplastic enzyme inhibitor, etastatic carcinoma of the colon or rectum	The mechanism of INT is similar to TPT. INT binds with cellular topo I–DNA complexes and has S-phasespecific cytotoxicity. The collision between the INT and Topo I complex with the replication fork also results in G2 arrest/delay by signalling the presence of DNA damage to an S-phase checkpoint mechanism. At more concentrations of irinotecan, non-S-phase cells can also be killed. The mechanism of non-S-phase cell killing appears to be related to transcriptionally mediated DNA damage and through apoptosis.[36]
5	Paclitaxel (PTX)	Taxus brevifolia Nutt.	Ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi's sarcoma, cervical cancer, and pancreatic cancer	PTX targets the microtubules. It promotes the polymerization of tubulin heterodimers to microtubules and suppresses microtubule changes resulting in mitotic arrest.[37,38]
6	Docetaxel (DTX)	Paclitaxel analog	Breast cancer, head and neck cancer, stomach cancer, prostate cancer and nonsmall-cell lung cancer.	DTX interferes with the normal function of microtubule growth. DTX is believed to have a two-old mechanism of antineoplastic activity: (1) inhibition of microtubular depolymerization, and (2) attenuation of the effects of bcl-2 and bcl-xL gene expression. Taxane-induced microtubule stabilization arrests cells in the cell cycle's G(2)M phase. It induces bcl-2 phosphorylation, promoting a cascade of events that ultimately leads to apoptotic cell death.[39,40]
7	Cabazitaxel (CTX)	Paclitaxel analog	Hormone-refractory prostate cancer	CTX is a new second-generation semi-synthetic microtubule inhibitor which induces cell death by microtubule stabilization. CTX binds to the N-terminal amino acids of the beta-tubulin subunit and promotes microtubule polymerization. During mitosis, microtubules spread near the mitotic spindle, which is responsible for the separation and distribution of chromosomes and cell division

				into daughter cells. CTX stimulates microtubule polymerization and inhibits microtubule cell division, thus arresting the tumor cell cycle and proliferation.[41]

Podophyllotoxins

The species Podophyllum peltatum L., commonly referred to as the American mandrake or mayapple, and Podophyllum emodii Wallich, native to the Indian subcontinent, have been traditionally used for medicinal purposes, including the treatment of skin cancers and warts. The primary active compound, podophyllotoxin, was first isolated in 1880, but its chemical structure was not fully described until the 1950s. Despite this, clinical trials of several related podophyllotoxin-like lignans did not succeed due to issues with effectiveness and significant toxicity. Subsequent extensive research led to the development of etoposide and teniposide, which have proven to be effective in clinical settings. In terms of their mechanism of action, while podophyllotoxin binds reversibly to tubulin, etoposide and teniposide function by inhibiting topoisomerase II, which results in DNA cleavage mediated by this enzyme. These drugs are currently used in the treatment of various cancers, including lymphomas, bronchial cancers, and testicular cancers. The development history of these agents, along with some related compounds currently under clinical investigation, has been reviewed.[42]

Table 2: Natural anti-cancer drugs and synthetic analogs.[17]

Sr.No.	Antitumor agent	Natural Source/ derivative	Applications and targets	Mechanism of Action (MOA)
1.	Podophyllotoxin (PTOX)	Podophyllum	Testicular, breast, pancreatic, lung, stomach, and ovarian cancers	Podophyllotoxin binds reversibly to tubulin, while etoposide and teniposide inhibit topoisomerase II. This inhibition-driven topo II-mediated DNA cleavage disrupts the dynamic balance between the assembly and disassembly of microtubules, ultimately resulting in mitotic arrest [43].
2.	Etoposide	Podophyllotoxin analog	Testicular and small cell lung tumors	Etoposide primarily prevents the DNA topo II, inhibiting DNA religation results in antagonistic-tumor venture. This causes a detracting problem in DNA combining at the premitotic stage of cellular division and can bring about tumor container apoptosis. Etoposide is container era-contingent and phase-particular, moving chiefly the S and G2 phases of cellular division. The etoposide-topoisomerase II complex starts a mutagenic and container death road, active best in lump containers with bigger levels of topo II enzymes.[44]
3.	Teniposide	Podophyllotoxin analog	Refractory childhood acute lymphoblastic leukemia	Similar to different PTOX analogs, it prevents type II topoisomerase project. Teniposide binds to and prevents DNA topoisomerase II. Teniposide's cytotoxic belongings believe the number of double-marooned DNA breaks created in containers, that indicate the stabilization of a topoisomerase II–DNA in-between.[45]

Microbial-Based Anti-Cancer Agents

Clinical tests have judged the favorable happening of new antagonistic-tumor drugs from microbial inceptions, and currently, many drugs are accessible on stock exchange.[46] In 1940, the finding of actinomycin from Streptomyces medicines (Streptomycetaceae offspring) altered the shades of antagonistic-tumor drug finding.[47] Streptomyces parvulus and additional Streptomyces variety exhibit important antagonistic-cancer characteristics. FDA certified various microbial-located crop, containing Bleomycin, Actinomycin D, Anthracyclines, Enediynes, Epothilones, and Mitomycin C, as antagonistic-malignancy drugs.[48] Among these ultimate appropriate and hopeful are anthracyclines, first unique from Streptomyces peucetius in the early 1960s, commonly famous as Daunorubicin and Doxorubicin. In 1980s, Enediynes, neocarzinostatin and calicheamicin were imported as antitumor and anticancer powers in display. Later, many added antagonistic-tumor microbial-located cures were grown, containing kedarcidina,

Dynemicin A, esperamicin, shishijimicin A, namenamycin, uncialamycin and maturepeptinam etc.[49]

Since 1954, Actinomycin D has happened secondhand as a chemotherapeutic agent for doctoring nephroblastoma (kind tumor) and Ewing's abnormal growth in animate being. Actinomycin D had various cytotoxic and antitumor endeavor machines: intercalation to DNA and maintaining cleavable composites of topoisomerases (topo) I and II accompanying DNA, photodynamic exercise and free radical establishment. Existing drug locks accompanying both DNA and RNA verbalization and by way of protein combining. Therefore, it induces basic p53-liberated apoptosis.[50] At present, Actinomycin D, Cosmegen and Lyovac are usable on stock exchange. In 1966, bleomycin (BLM) was found in Streptomyces verticillus. It was started on stock exchange in 1969 in Japan and in 1973 in the USA.[51] BLM induces the oxygen and hardware ion-weak cleaving of DNA. BLM binds to DNA and iron (II) and hydroxyl radicals are freed under the influence of microscopic oxygen, developing in DNA damage and Fe(II) corrosion.[52] It is a cytotoxic medicine used to recognize testicular tumor, cervical malignancy, ovarian malignancy, Hodgkin's lymphoma and non-Hodgkin's lymphoma. BLM drugs to a degree Bleomycin USP and Blenoxane are accessible concerning business.

Table 3: Natural anti-cancer drugs and synthetic analogs.[17]

Sr.No.	Antitumor agent	Natural Source/ derivative	Applications and targets	Mechanism of Action (MOA)
1.	Bleomycin (BLM)	Streptomyces verticillus	Head and neck malignancy, lymphoma, and testicular tumors, among others	Etoposide binds to guanosine-cytosine-rich portions of DNA by way of "S" tripeptide through prejudiced intercalation of the bithiazole rings. The free radicals of ETP belongings DNA distinct-fiber break at 3'-4' bonds in deoxyribose. This produces free advance to first base propenals, particularly thymine and cytotoxicity is cellcycle-stage particular for G2 stage. The DNA-cleaving conduct of BLM is helpless on oxygen and mineral ions.[53]
2.	Dactinomycin (DCM)	Streptomyces	Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasm, testicular cancer, and certain types of ovarian cancer	DNA intercalation and restriction of RNA (stop of RNA polymerase elongation) and protein combining are container era stages nonspecific.[54]
3.	Doxorubicin (DXB)	Streptomyces peucetius var. caesius	Breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukaemia	DXB covers the drug's efficiency by intercalating inside DNA base pairs, making DNA rope breakages and inhibiting two together DNA and RNA combining. Doxorubicin prevents the something which incites activity topo II, provoking DNA damage and inference of apoptosis.[55]
4.	Daunorubicin (DNB)	Streptomyces	Acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myelogenous leukaemia, and Kaposi's sarcoma	DNB forms a complex accompanying DNA by way of intercalation middle from two points base pairs. It restricts topo II exercise by sustaining the DNA-topo II complex and staying the religation unspecified the topo II backlash catalyzes, happening in distinct and double-fiber breaks, accordingly inhibiting DNA and RNA combining.[56]

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