Role of Natural Products in Developing Novel Anticancer Agents: 
A Perspective

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Cancer is a heterogeneous disease and is one of the significant health issues, especially in public health systems around the world. Natural products and their structural derivatives with outstanding chemical diversity have been investigated for potential anti-cancer agents. Many natural products revealing potential anti-cancer properties such as cytotoxicity, proliferation inhibition, induced apoptosis, retard metastasis, suppressing angiogenesis, and improved chemotherapy have been isolated from various plants and herbs. Several promising lead molecules have been identified recently; a few are in the clinical trial stage. This short communication summarises the role of natural products and their analogs in anti-cancer drug developments, especially plant, marine and microbial-based anti-cancer agents.

Keywords: natural products, cytotoxicity, chemotherapy, anti-cancer.

1. Introduction

Nature is an inexhaustible renewable source of novel pharmacophores, chemotypes and many therapeutic agents. Many modern drugs have been developed from natural products (NP). [1 – 3] More than 50% of the approved drugs are natural source-based. [4] The modern drug design and discovery era has three significant sources of novel compounds: original natural products, structurally mimicking semi-synthetical natural products and chemically synthetic molecules based on the natural product model. [5, 6]

Considering the earliest scientific reports on the behaviour of cancer, in 1762, Giovanni Battista Morgagni, the father of modern anatomical pathology, first identified cancer behaviour. He autopsied a corpse for the first time to determine the relationship between the patient’s sickness and pathologic observations. Giovanni’s studies reported the basis of scientific cancer strategies. [7] John Hunter, a Scottish surgeon, introduced the surgery strategies for cancer patients whose tumors have no invasive and moveable features to close sites; he mentioned: “there is no impropriety in removing it”. [8] In the 20th century, sentient developed radiotherapy and surgery as the two dominant strategies to treat and diagnose cancer diseases. [9] The term “chemotherapy” was first used and introduced by a famous German chemist, Paul Ehrlich, in the early 1900s, and it states the therapeutic use of chemicals to treat diseases. [10]

Cancer is one of the most common global devastating diseases affecting the public health system. Furthermore, cancer is estimated as the second leading cause of mortality in humans. [11 – 14] In 2020, WHO reports approximately 25 million new cases and around 10 million deaths of cancer were reported worldwide. The most common death of cancer follows breast (2.26 million cases); lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.09 million cases). [15] Researchers have isolated many novel natural molecules from plants, microbes, and other living organisms to evaluate their anti-cancer activity and mechanism of action. These complex works have led to the discovery of novel anti-cancer drugs. Natural products from...
various sources portend the ability to increase several physiological pathways essential for treating and diagnosing diseases, including cancer.\[16,17\] According to literature reports, more than 65% of synthetic drug molecules are derived from nature, and most of the natural active drugs, especially from plant sources, establish 75% of anti-cancer drugs.\[18\]

The list of the anti-cancer synthetic derivatives based on plant sources includes Camptothecin and analogs, Belotecan (Camptobells); Paclitaxel (Taxols) and the analogs Docetaxel (Taxoteres), Vinblastine (Velbans); Podophyllotoxin and analogs, Etoposide (Etopophoss) and Teniposide (Vumons); Vincristine (Oncovins) and their analogs, Vindesine (Eldisines), Cabazitaxel (Jevtanas), Irinotecan (Camptosars), Topotecan (Hycamtins), and Vinorelbine (Navelbines).\[19 – 21\] The bacteria derived from the soil are also incredible sources of anti-cancer drugs such as anthracyclines, Doxorubicin (Doxils; Adriamycins), Nonribosomal peptide, Dactinomycin (Cosmegens), Daunorubicin (Cerubidines), Epirubicin (Ellences) and Glycopeptide bleomycin (Blenoxanes) (Figure 1).\[22,23\]

Natural products possess anti-cancer activity because of natural antioxidants that act as reducing agents, singlet oxygen quenchers, and free radical scavengers. The leading cause of their antioxidant nature is the bioactive compounds such as flavonoids, lignans, flavones, coumarins, isoflavones, anthocyanins, isocatechin, and catechins. In addition, natural products can effortlessly reduce and mitigate the toxic side effects from radiation and chemotherapy treatment.\[24 – 26\] Rapid growth in cancer biology, immunology, and genetics has promoted the development of several new drugs on the market. Almost 700 cancer-related drugs are currently under different phases of clinical and preclinical testing, and nearly 100 drugs have been approved and are currently on the market. The FDA has approved 37 drugs for current usage.\[27,28\]

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2. Plant-Based Anti-Cancer Agents

The most promising natural source, plants, are grown to biosynthesis various biologically active compounds, including pretty small drugs and molecules or derivatives with rich steric complexity (e.g., taxol) to survive as the most promising therapeutic molecules for various diseases.\(^{[29]}\) The history and background of using plant species for cancer treatment can be identified back to Ebers papyrus in 1500 BC. However, the systematic exploring anti-cancer lead molecules from plant species for modern drug development started only in the early 20\(^{th}\) century.\(^{[30,31]}\) Plant-derived natural products have been the primary source of various structurally relevant anti-cancer agents and will continue to develop novel chemical agents in cancer drug developments. Many plant-based cancer drugs are marketed, while a few are in clinical trial stages (Table 1). Among those agents, Paclitaxel (PTX), a drug obtained from the bark of Taxus brevifolia, presents one of the most successful stories in anti-cancer drug discovery.\(^{[32]}\) Many researchers have paid great attention to plant-derived anti-cancer drugs. Broadly, four main classes of natural products are used in cancer treatment. These include (i) camptothecin derivatives (irinotecan and topotecan),\(^{[33]}\) (ii) Vinca (Catharanthus) bisindole alkaloids (vinblastine, vincristine, vinorelbine and vinflunine),\(^{[34]}\) (iii) taxanes (paclitaxel and paclitaxel albumin-stabilized nanoparticle formulation, docetaxel and cabazitaxel), and (iv) semi-synthetic epi-podophyllotoxins (etoposide, etoposide phosphate and teniposide), (Figure 2).\(^{[35]}\) Many articles on isolating and identifying plant species with anti-cancer activity have been reported. Most of these findings were at the preliminary screening level using in vitro assay or cell lines and cytotoxicity assays using several human cancer cell lines.

The vinca alkaloids (Vincristine and Vinblastine) bind to a specific site of tubulin heterodimers (vinca-binding site) and either disrupt the microtubule functions or arrest the cell cycle at metaphase. Several semi-synthetic derivatives of vinca alkaloids have been introduced into the market. These alkaloid derivatives are applied alone or combined with other phytochemical agents to fight against different cancers.\(^{[36,37]}\)
| S. No. | Antitumor agent | Natural Source/derivative | Applications and targets | Mechanism of Action (MOA) |
|-------|-----------------|----------------------------|--------------------------|---------------------------|
| 1     | 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.\[^{57,58}\] |
| 2     | Docetaxel (DTX)  | Paclitaxel analog          | Breast cancer, head and neck cancer, stomach cancer, prostate cancer and non-small-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.\[^{59,60}\] |
| 3     | 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.\[^{61}\] |
| 4     | 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 relevation 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.\[^{62}\] |
| 5     | 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 relocation 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.\[^{63}\] |
| 6     | Topotecan (TPT)  | *Camptothecin* analog      | Ovarian cancer | The MOA of TPT acts by making a stable covalent complex with the DNA/topo I aggregate. This so-called 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.\[^{64}\] |
| 7     | Irinotecan (INT) | *Camptothecin* analog      | Antineoplastic enzyme inhibitor, metastatic 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-phase-specific 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.\[^{65}\] |
| S. No. | Antitumor agent (Natural Source/derivative) | Applications and targets | Mechanism of Action (MOA) |
|-------|------------------------------------------|--------------------------|--------------------------|
| 8     | Vinblastine (VBS) *Vinca rosea L.* | Breast cancer, testicular cancer, neuroblastoma, Hodgkin’s and non-Hodgkins lymphoma, mycosis fungoides, histiocytosis, and Kaposi’s sarcoma | The MOA of VBS is understood to be primarily due to mitosis inhibition at metaphase by its interaction with tubulin. Vinblastine binds to the microtubular proteins of the mitotic spindle, crystallizing the microtubule. It leads to mitotic arrest or cell death. \cite{66,67} |
| 9     | Vincristine (VCS) *Vinca rosea L.* | Leukemia, malignant lymphoma, Hodgkin’s disease, acute erythraemia, and acute pancytopenia | 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. \cite{68} |
| 10    | Vindesine (VDS) | Acute lymphocytic leukemia | Vindesine binds to the microtubular proteins of the mitotic spindle, leading to microtubule crystallization and mitotic arrest or cell death. \cite{69} |
| 11    | Vinorelbine (VRB) *Vincristine analog* | Metastatic non-small cell lung carcinoma | Vinorelbine main targets are tubulin and microtubules. It stimulates microtubule depolymerization and mitotic spindle obliteration at high concentrations, whereas, at lower concentrations, it can block mitotic progression. VRB binds to β-tubulin subunits at the Vinca-binding area nearby the constructive end of microtubules. The rapid and reversible binding by Vinorelbine to soluble tubulin induces a conformational change that increases the affinity of tubulin for itself. This plays a vital role in the kinetics of microtubule stabilization. \cite{70} |
| 12    | Podophyllotoxin (PTOX) *Podophyllum* | Testicular, breast, pancreatic, lung, stomach, and ovarian cancers | Podophyllotoxin reversibly binds to tubulin, etoposide and teniposide and inhibits the topo II. This inhibition-induced topo II-mediated DNA cleavage interrupts the dynamic equipoise between the assembly and disassembly of microtubules and finally causes mitotic arrest. \cite{71} |
| 13    | Etoposide *Podophyllotoxin analog* | Testicular and small cell lung tumors | Etoposide mainly inhibits the DNA topo II, inhibiting DNA religation results in anti-cancer activity. This causes a critical problem in DNA synthesis at the premitotic stage of cell division and can lead to tumor cell apoptosis. Etoposide is cell cycle-dependent and phase-specific, affecting mainly the S and G2 phases of cell division. The etoposide-topoisomerase II complex triggers a mutagenic and cell death pathway, working best in tumor cells with higher levels of topo II enzymes. \cite{72} |
| 14    | Teniposide *Podophyllotoxin analog* | Refractory childhood acute lymphoblastic leukemia | Similar to other PTOX analogs, it inhibits type II topoisomerase activity. Teniposide binds to and inhibits DNA topoisomerase II. Teniposide’s cytotoxic effects depend on the number of double-stranded DNA breaks produced in cells, which reflect the stabilization of a topoisomerase II–DNA intermediate. \cite{73} |
| 15    | Bleomycin (BLM) *Streptomyces verticillus* | Head and neck malignancy, lymphoma, and testis | Etoposide binds to guanosine-cytosine-rich portions of DNA via “S” tripeptide through partial intercalation of the bithiazole rings. The free radicals of ETP effects DNA single-strand break at 3’-4’ bonds in deoxyribose. This produces free base propenals, especially thymine and cytotoxicity is cell-
Table 1. (cont.)

| S. No. | Antitumor agent | Natural Source/derivative | Applications and targets | Mechanism of Action (MOA) |
|-------|-----------------|---------------------------|--------------------------|---------------------------|
| 16    | Dactinomycin (DCM) | *Streptomyces* | Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasm, testicular cancer, and certain types of ovarian cancer. | Cycle-phase specific for G2 phase. The DNA-cleaving actions of BLM is dependent on oxygen and metal ions.\(^{[74]}\) DNA intercalation and inhibition of RNA (prevention of RNA polymerase elongation) and protein synthesis are cell cycle phases nonspecific.\(^{[75]}\) |
| 17    | Doxorubicin (DXB) | *Streptomyces peucetius var. caesius* | Breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia | DXB comprises the drug's capability by intercalating within DNA base pairs, forming DNA strand breakages and inhibiting both DNA and RNA synthesis. Doxorubicin inhibits the enzyme topo II, causing DNA damage and induction of apoptosis.\(^{[76]}\) |
| 18    | Daunorubicin (DNB) | *Streptomyces* | Acute myeloid leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, and Kaposi's sarcoma | DNB forms a complex with DNA via intercalation between base pairs. It inhibits topo II activity by stabilizing the DNA-topo II complex and stopping the religation part of the topo II reaction catalyzes, resulting in single and double-strand breaks, thus inhibiting DNA and RNA synthesis.\(^{[77]}\) |
| 19    | Epirubicin Doxorubicin analog | Primary breast cancer | Epirubicin forms complexes with DNA by intercalation between base pairs. It inhibits topo II activity via stabilizing the DNA-topo II complex, avoiding the religation portion of the ligation-religation reaction that topo II catalyzes. It also interferes with DNA replication and transcription by inhibiting DNA helicase activity.\(^{[78]}\) |
| 20    | Mifamurtide Muramyl dipeptide derivative | Resectable, non-metastatic osteosarcoma after surgical resection | Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE) is a synthetic derivative of muramyl dipeptide (MDP), the smallest naturally-occurring immune stimulatory component from the cell walls from Mycobacterium sp. MTP-PE is a specific ligand of nucleotide-binding oligomerization domain (NOD) 2 receptor, a receptor found primarily on monocytes, dendritic cells and macrophages. It possesses an amino-terminal caspase recruitment domain, which is required to trigger nuclear factor-kappa B (NF-κB) signalling. Activation of intracellular signalling transduction pathway NF-κB can promote inflammation and release of antimicrobial peptides, resulting in the production of pro-inflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and TNF-α, and other molecules such as chemokines and adhesion molecules.\(^{[79]}\) |
These drugs possibly inhibit the cell cycle transition from metaphase to anaphase, causing cell cycle arrest and apoptosis. Paclitaxel reduces cancer cell reproduction as it polymerizes or stabilizes the microtubules in the cells. Paclitaxel is one of the primary drugs to have a more effect on cancer diagnosis, and Vincristine and Vinblastine were two of the initial drugs to be isolated. Different analogs of paclitaxel include Larotaxel, Orptataxel, Milataxel and Tesetaxel, which are currently under clinical trials. Larotaxel is used alone or in combination with other therapies for urethral bladder, pancreatic, lung and breast cancer.

A combination of drugs derived from Vinca, Podophyllum lignans, Taxus diterpenes, and Camptotheca alkaloids from the plant extracts may increase their anti-cancer activity and enhance their effectiveness as therapeutic agents. The investigation of Solowely et al. showed that the plant extracts with a combination of anti-cancer compounds could have killing activity on specific cancer cell lines. It displayed no effect on normal human lymphocytes and fibroblasts. This report describes that plant extracts are more valuable as therapeutic agents than chemically derived ones, which cause toxic complications in cancer treatment. The plant extracts induced apoptosis, which was demonstrated by an increased sub-G1 phase population of cells with lower DNA content and condensation of chromatin. Also, Caspase 3 activation was observed after extract treatment, which is a crucial stage in apoptotic cell death.

3. Microbial-Based Anti-Cancer Agents

Clinical trials have evaluated the successful development of new anti-cancer drugs from microbial origins, and currently, many drugs are available on the market. In 1940, the discovery of actinomycin from Streptomyces antibiotics (Streptomycetaceae family) changed the shades of anti-cancer drug discovery. Streptomyces parvulus and other Streptomyces species exhibit significant anti-cancer properties. FDA approved several microbial-based products, including Bleomycin, Actinomycin D, Anthracyclines, Enediynes, Epothilones, and Mitomycin C, as anti-cancer drugs (Figure 3 and Table 1). Among these the most relevant and promising are anthracyclines, first isolated from Streptomyces peucetius in the early 1960s, commonly known as Daunorubicin and Doxorubicin. In 1980s, Enediynes, neocarzinostatin and calicheami-
cin were introduced as antitumor and anticancer agents in market. Later, many other anti-cancer microbial-based medicines were developed, including kedarcidina, Dynemicin A, esperamicin, shishijimicin A, namenamycin, uncialamycin and maturepeptinam etc.\cite{42}

Since 1954, Actinomycin D has been used as a chemotherapeutic agent for treating nephroblastoma (kidney cancer) and Ewing's sarcoma.\cite{45} Actinomycin D had different cytotoxic and antitumor activity mechanisms: intercalation to DNA and stabilizing cleavable complexes of topoisomerases (topo) I and II with DNA, photodynamic activity and free radical

Figure 3. Chemical structures of microbial-based anti-cancer drugs.
formation. Existing drug locks with both DNA and RNA expression and as a consequence protein synthesis. Therefore, it induces cellular p53-independent apoptosis. At present, Actinomycin D, Cosmegen and Lyovac are available on the market. In 1966, bleomycin (BLM) was discovered in *Streptomyces verticillus*. It was launched on the market in 1969 in Japan and in 1973 in the USA. BLM induces the oxygen and metal ion-dependent cleaving of DNA. BLM binds to DNA and iron (II) and hydroxyl radicals are released under the influence of molecular oxygen, resulting in DNA damage and Fe(II) oxidation. It is a cytotoxic antibiotic used to diagnose testicular cancer, cervical cancer, ovarian cancer, Hodgkin’s lymphoma and non-Hodgkin’s lymphoma. BLM drugs such as Bleomycin USP and Blenoxane are available in the market.

Mitomycin C was introduced in the 1950s by *Streptomyces caespitosus* species as an antitumor antibiotic by stopping its synthesis. Mitomycin C is used to treat cervical, breast, head, anal, liver, bladder, colorectal, lung, pancreas and stomach cancers. Currently, Mitomycin Accord and Mitomycin C Kyowa are available on the market. In 1974, doxorubicin (DOX), an anticancer/antitumor antibiotic agent, was isolated from *Streptomyces peucetius* and was first commercially introduced in the USA market as one of the most effective anti-cancer drugs from the microbial community for the treatment of lymphoma, breast, Kaposi’s sarcoma, acute lymphocytic leukaemia and bladder cancers. The mechanism of DOX includes: (i) intercalation between the base pairs of the DNA strands and inhibition of the synthesis of DNA and RNA in rapidly growing cells by blocking the replication and transcription processes; (ii) generation of iron-mediated free radicals, causing oxidative damage to cellular membranes, proteins and DNA.

4. Marine Organisms-Based Anti-Cancer Agents

For the past few decades, plants and microbial-based natural products have dominated the successful journey of modern anti-cancer drug development. Further, marine organisms, mainly marine sponges, have also provided anti-cancer drugs. Various marine-based anti-cancer agents exhibit potential human cancer cell growth inhibition *in vitro*, and many *in vivo* murine models and humans have been isolated. Most of these agents have entered clinical trials in cancer. Examples of these drugs include cytarabine (Ara-C), monomethyl auristatin E, Yondelis®, halichondrin B, eribulin and Adcetris® (Figure 4). The first marine anti-cancer natural agent, Trabectedin (also

![Figure 4. Marine organism-based anti-cancer drugs.](image-url)
called Ecteinascidin-743), was isolated from Ecteinascidia turbinate in 1984. It has been developed as a chemotherapeutic agent known as Yondelis (brand name) to treat ovarian cancer and advanced soft tissue sarcoma. The macrocyclic polyether halichondrin B was isolated from different marine sponge species, Halichondria okadai, Axinella spp. and Phakellia spp. The molecules were also the basis for another anti-cancer drug, eribulin mesylate (E7389). The drug was approved in 2010 and marketed as Halaven® as an effective agent for metastatic breast cancer chemotherapy.\textsuperscript{52} Antimitotic polypeptide synthetic analog, Monomethyl auristatin E, belongs to a class of dolastatins, which was first isolated from Dolabella Auricularia (Phylum Mollusca).\textsuperscript{53} However, cytarabine is not exactly obtained from natural sources. It was synthesized using the nucleoside from the Tectitethya crypta (Caribbean sponge) as a synthesis model. This drug was approved in 1972 to treat leukaemia and a variety of lymphoma cancers.\textsuperscript{54}

Chinese researchers have made remarkable contributions to advancing natural products in cancer treatment, especially in marine and plant products. A range of botanical bioactive agents has been identified against cancer targets, such as Hematoxylin, Eucalyptin, Pseudolaric acid B, Parthenolide, Trabectedin, and Ulocladol (Figure 5). Hematoxylin and its derivatives extracted from woods of Haematoxylon campechianum, are reported to be ATP competitive inhibitors of broad-spectrum protein tyrosine kinases, with excellent IC\textsubscript{50} at nanomolar concentrations.\textsuperscript{55} Eucalyptin A, isolated from the fruits of Eucalyptus globulus Labill, reveals a potential inhibitory effect in c-Met/HGF axis.

Natural products have contributed significantly to anti-cancer drug discovery. There has been substantial research establishing the anti-cancer activity of several natural products on different cancer cell lines. The results confirm that natural products are the lead molecules for many new anti-cancer drugs. Nature-derived molecules have a high impact as chemotherapeutic agents, alone or in combination with other conventional medicines. The conjugation of potential natural products to monoclonal antibodies for targeting specific epitopes on cancer tumors offers another promising tool for developing active chemotherapeutic agents. Many novel hit molecules are from various natural sources that paved paths for developing new and effective anti-cancer agents.

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Figure 5. Chemical structures of biologically active anti-cancer agents.
Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
Data sharing does not apply to this article as no new data were created or analyzed in this study.

Author Contribution Statement
B.B.S. performed the literature survey, analyzed the data and prepared the draft. N.K.K developed the concept and contributed to the data analysis. S.B.J reviewed the draft and finalized the manuscript.

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