



Review Article

Anti-cancer agents from natural sources: A review

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ABSTRACT

The natural products have played a dominant role in the treatment of human ailments. The discovery of penicillin has changed the scenario of modern medicine. With the ancient use of quinine for malaria, willow bark for pain and several other natural products used as medicines in ancient system of medicine such as Ayurveda and traditional China, the discovery of the medicines for the allopathic use from natural source has gained substantial attention. The ancient system of Ayurveda describes the used of many plants extracts being used for the treatment of cancer. Prevailing epidemiological factors have also described the use of the mediterranean diet and inclusion of fruits and vegetables to score low as risk factor for the cancers. Further the several discoveries have led to the transformation of the active constituents of the natural products from the dietary sources for the chemoprevention. Substantial trials in the development of the drugs from the marine and microbial origin have been fruitful and positive to develop safe and efficacious drugs. However, the success being very low due to unavailability of natural products in large gram amounts required for the clinical trials. The total synthesis of many natural products from marine origin has also emerged to solve this issue and led to successful development of 4 marine drugs as anti-cancer agents. This overview reviews the anticancer drugs from the natural origin as the chemo preventive and chemotherapeutic agents. Wherever possible the details of the clinical trials have been discussed along with uses and mechanism of action.

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1. Introduction

The drugs from the natural origin, i.e. natural products have played significant role in treatment of human ailments. Since ancient times the use of salicylates for the treatment of pain from the willow and the quinine from cinchona for the treatment of malaria are the most prevalent examples for the use of natural products in treatment of human infections and ailments. The projected incidence of patients with cancer

in India among males was 679,421 (94.1 per 100,000) and among females 712,758 (103.6 per 100,000) for the year 2020. One in 68 males (lung cancer), 1 in 29 females (breast cancer), and 1 in 9 Indians will develop cancer during their lifetime.¹ Cancer chemoprevention uses medicines from the synthetic or natural origin to inhibit, retard, or reverse the process of carcinogenesis.²⁻⁴ The natural product use for therapeutics is still one of the most prevalent in addition to the traditional remedies as exemplified by the legendary discovery of penicillin. Drugs from natural origin still comprise a large part of the day to day therapies. The

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vaccine development for the cancer is still a dream however for certain cancers such as cervical cancers the vaccines are available.^{5,6} The cancer chemotherapy depends on the early diagnosis, treatment in cases of non-metastatic cancers and solely on chemotherapy for the metastatic cancers. The role of drugs of natural origin and their use in cancer has been overviewed.

2. Cancer Chemotherapy and the Role of Natural Products

Over 60% of the current anticancer drugs were derived in one way or another from natural sources. Nature is full of abundance with natural compounds with active chemical constituents that may effectively work against cancer. There are some methodologies that are being followed for to the natural product drugs for the treatment of cancer and these include one of the following methods:

1. **Extract:**^{7–9} Sometimes the part of plant extract is being used for the treatment of cancers as the case may be, however this type methodology is least followed now a day in allopathic practice where the active constituent must be labelled. However, this type of formulation is most commonly seen in Ayurveda.^{10,11}
2. **Isolate:** This is label claim and most of the extracts have been isolated to their active constituent for the treatment of the cancer and widely accepted practice according to any FDA regulation.^{12–15}
3. **Semi-synthetic modification:** The most of the active constituents after they have been isolated are semi-synthetically modified to give rise to the form of semisynthetic natural product for the cancer therapeutics.^{16–19}
4. **Synthetic modification:** The new advances in synthetic chemistry of natural products and drug design have been enabling the total synthesis of the many natural products and these can be used where the amount of actual natural product isolate is very low.^{20–22}
5. **Formulation improvements:** Most of the natural products are poorly soluble and cannot be absorbed from the GI tract, in such cases many formulation improvements are being made so that these drugs become more absorbable and more patient compliant.^{23–25}
6. **Conjugates:** Tagging of natural products with the monoclonal antibodies is being practiced and it has been shown to be effective in treatment and targeting the epitopes on the tumor.
7. It should be noted that effective cancer chemotherapy often involves the use of combinations of several agents (so-called combination chemotherapy), and these combination regimens can comprise agents derived from both natural and synthetic sources.^{26–28}

2.1. Terrestrial plants as anti-cancer agents^{29–31}

Historically, successfully implementation of some terrestrial plant derived agents have been sought and these plant-derived agents include VBL and vincristine (VCR), etoposide, paclitaxel, docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available. However they come with side effects of toxicity and formulation problems such as poor solubility and have been succeeded and widely used in chemotherapeutics for the cancer treatment. *Vinca Alkaloids*^{32,33}

2.1.1. Vincristine and vinblastine

The plant was used by various cultures for the treatment of diabetes, however when extracts were investigated in rats, they were found to demonstrate reduction in white blood cell count and showed profound bone depression.

Vincristine and Vinblastine are alkaloids derived from the plant, *Catharanthus roseus* G. Don. (Apocynaceae), a Madagascar periwinkle. Also known as *Vinca* alkaloids. They are active against lymphocytic leukemia in mice. Mechanism of action is disruption of microtubules causing arrest of cells at metaphase and apoptotic cell death.

2.1.2. Semisynthetic analogues^{34,35}

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. Anhydrovinblastine belongs to the class of organic compounds known as *vinca* alkaloids. These are alkaloids with a dimeric chemical structure composed of an indole nucleus (catharanthine), and a dihydroindole nucleus (vindoline), joined together.

2.1.2.1. Uses. In combination with other chemotherapeutic agents used for variety of malignancies such as leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. *Podophyllotoxins*^{36,37}

2.1.3. Etoposide and teniposide

It was used in Indian subcontinent as *Podophyllum emodii* Wallich for treatment of skin cancers and warts. First isolated in 1880 and was then later reported in 1950s. Also obtained from the species *Podophyllum peltatum* L. (commonly known as the American mandrake or mayapple).

Clinical trials of several closely related podophyllotoxin-like lignans, however, failed due to lack of efficacy and unacceptable toxicity. The extensive research on the structure led to the development of etoposide and teniposide as clinically effective agents. Mechanism of action shows that, podophyllotoxin reversibly binds to tubulin, etoposide and teniposide inhibit topoisomerase II, inducing topoisomerase II-mediated DNA cleavage.

2.1.3.1. Uses . Lymphomas, and bronchial and testicular cancers. *Taxanes*^{38–41}

In Ayurvedic medicine system, *Taxus baccata* is used for the treatment of the cancers. Other sources of the Taxanes which include paclitaxel and obtained and isolated from originally isolated from the bark of the Pacific yew, *Taxus brevifolia* Nutt. (Taxaceae), and docetaxel , a semisynthetic analogue synthesized from DAB (10-deacetylbaaccatin III) isolated from the leaves of the European yew, *Taxus baccata* .

2.1.4. Paclitaxel and docetaxel

DAB is semi-synthetically converted to paclitaxel. Mechanism of action of these taxane derivatives is that they promote the polymerization of tubulin heterodimers to microtubules, suppressing dynamic changes in microtubules resulting in mitotic arrest.

2.1.4.1. Uses . It is used in 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.

Substantial synthetic modifications in the structure of taxanes have resulted in the development of variety of analogues. Some of the clinical limitations of paclitaxel and docetaxel, include poor solubility, allergic reactions, dose-limiting toxicities such as myelosuppression or peripheral sensory neuropathy, and the development of drug resistance due to P-glycoprotein-mediated efflux. *Cabazitaxel*⁴² It is approved for the treatment of metastatic prostate cancer (in combination with prednisone and/or prednisolone).

Some of the structural analogues in clinical development are given as follows: *Taxoprexin*⁴³ or 7-docosahexaenoic acid (DHA)-paclitaxel (Protarga), a prodrug of paclitaxel covalently bound to the naturally occurring ω -3 fatty acid DHA which enables delivery directly to tumor tissue.

Larotaxel (XRP9881); *Ortataxel*.⁴⁴ *Tesetaxel*.⁴⁵ (DJ-927); TPI-287, and paclitaxel poliglumex (PPX, CT-2103) an α -poly- L -glutamic acid conjugate of paclitaxel.⁴⁶ It is a potent radiation sensitizer, possibly enhancing radiation for glioblastoma.

The approved formulations of nanoparticle paclitaxel are mentioned as follows:

2.1.5. Nab-paclitaxel

It is an albumin-stabilized nanoparticle formulated without the use of emulsifying agent.

2.1.6. Cremophor (polyethoxylated castor oil):⁴⁷

It is a formulation of paclitaxel enabling larger doses of paclitaxel to be administered while avoiding the toxic effects associated with Cremophor.

2.1.6.1. Uses . It is used in refractory breast cancer, NSCLC, and pancreatic cancer as a less toxic agent,

although it is less effective, alternative to the 4-drug regimen (leucovorin, 5-FU, irinotecan, and oxaliplatin).

2.1.6.2. Genexol-PM:^{47,48}. A Cremophor EL-free polymeric micelle formulation of paclitaxel, which has shown activity against gemcitabine sensitive and -resistant pancreatic ductal adenocarcinoma cell lines.

2.1.6.3. Tocolol (S-8184):⁴⁹. A tocopherol based Cremophor-free formulation of paclitaxel It has higher bioavailability of unbound paclitaxel compared to Cremophor EL-formulated paclitaxel.

2.1.6.4. Camptothecins⁵⁰. The source for Camptothecins (CPTs) as active constituent is the Chinese ornamental tree *Camptotheca acuminata* Decne (Nyssaceae). The acts by 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. The water-soluble sodium salt in the 1970s, was discovered and clinical trials however, were terminated due to severe bladder toxicity. Comprehensive reviews of CPT and its analogues have been published. The chemical structure study and modifications led to the development of semisynthetic derivatives, topotecan, irinotecan and belotecan , approved for clinical use. To avoid the problems of bioavailability , toxicity and pharmacokinetics, many structural analogues of CPT have been designed and developed.

2.1.7. Cositecan and silatecan (AR-67)

These are lipophilic silicon-containing CPTs modified in the gimatecan 7-position^{51,52}

2.1.8. Diflomotecan and derivatives ((BN80915), 10,11-difluorohomo CPT)^{53,54}

It is Water-soluble diflomotecan analogue currently in clinical development are the hydrochloride salts of elemotecan, lurtotecan, and namitecan, as well as DRF-1042.

2.1.9. SN-38 (7-ethyl-10-hydroxy CPT)⁵⁵

It is a poorly soluble in water and pharmaceutically approved solvents. The extensive research on formulation using macromolecules and these agents for delivery to the cancer cells and tissues, thus improving efficacy and reducing side effects.

2.1.10. Products derived from CPT⁵⁶

2.1.10.1. CRLX101 . It is conjugated form of polymeric nanoparticle cyclodextrinpoly(ethylene glycol) copolymer, with apparent solubility increase of >1,000-fold as compared to CPT. It shows excellent safety, pharmacokinetic, and efficacy results in an early clinical

trials in patients with advanced solid malignancies.

2.1.10.2. XMT-1001 (MER-1001 or PHF-CPT) . It is a novel, water-soluble macromolecular prodrug of CPT (molecular weight:70 kDa), in which CPT is conjugated to a hydrophilic, biodegradable polyacetal polymer, poly(1-hydroxymethylethylene hydroxymethylformal), also known as PHF and is slowly released.

2.1.11. Combretastatins⁵⁷

The combretastatins are a family of stilbenes originally isolated from the root bark *Combretum caffrum*, also known as the Cape bush willow in southern Africa. Mechanism of action of the drugs include it act as vascular disrupting agents, selectively targeting the endothelial cells lining the tumor vasculature. They also disrupt the tubulin cytoskeleton and remodel the actin cytoskeleton, inducing a significant change in the three-dimensional shape of immature endothelial cells, thereby stopping blood flow through the capillary and starving the tumor of nutrients, causing tumor cell death. This mechanism of action differentiates the combretastatins from angiogenesis inhibitors that are designed to work by preventing the growth of new blood vessels.

2.1.12. Combretastatin prodrugs⁵⁸

Combretastatin A4 phosphate is a phosphate prodrug of CA4. It was granted orphan drug status for the treatment of anaplastic thyroid cancer, medullary thyroid cancer, and stage IV papillary or follicular thyroid cancer. Used for the treatment of ovarian cancer, and treatment of patients with platinum-resistant ovarian cancer with a combination of CA4P, carboplatin. Numerous analogues of Combretastatin A4 phosphate such as Combretastatin A1 diphosphate is a phosphate prodrug of CA1 ,and found to be promising in relapsed and refractory acute myelogenous leukemia (AML) and myelodysplastic syndrome patients . It received orphan drug designation for the treatment of AML.

2.1.13. Homoharringtonine (HHT) (*Omacetaxine Mepesuccinate*)^{59,60}

It was isolated first in 1970 from the Chinese tree, *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.; Cephalotaxaceae). The bark of this plant was used in traditional medicine in china for various conditions. In 1983, it was reported to have significant cytotoxicity of the total alkaloid fraction of *Cephalotaxus fortunei* Hook F. A racemic mixture of HHT and harringtonine has been used in China for the treatment of AML and chronic myelogenous leukemia (CML). The principal mechanism of action of HHT is the inhibition of protein synthesis in a dose- and time-dependent manner by acting on the ribosomes of cancer cells. It blocks the progression of cells from G1 phase into S phase and from G2 phase

into M phase. It is showed synergistic or additive in vitro with AraC, amsacrine, actinomycin D and dexamethasone. Clinical studies have indicated that HHT is effective in treating acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS), but not acute lymphoblastic leukemia (ALL) and solid tumors. The dose limiting toxicities are hypotension and myelosuppression. Homoharringtonine has relatively mild extramedullary toxicities and no anthracycline-like cardiac toxicity, which make it a suitable candidate for the treatment of aged patients. Pharmacological studies indicate that HHT belongs to the category of multidrug resistance (MDR)-related drugs.

2.1.14. Ingenol Mebutate (*Ingenol-3-Angelate*)^{61,62}

It is obtained from the plant *Euphorbia peplus* (Euphorbiaceae) is widely used as a home remedy for the treatment of various skin conditions, and clinical studies. The crude *E. peplus* sap in the 1970s showed positive and promising pharmacological activity. The active chemical constituents include hydrophobic diterpene ester, ingenol-3-angelate (PEP005; ingenol-3-mebutate; Picato). It is believed to act through activation of protein kinase C(PKC). FDA approved it in year 2012, as a topical gel formulation (Picato) for the EMA.

2.2. Anticancer agents discovered from marine source⁶³

Sea covers 70% of the planet and out of which less than 5% have been explored for the pharmacological activity and less than 0.01% of the deep sea have been explored for the pharmacological flora and fauna. Only 4 drugs from the marine origin have been approved for the human use which are from the marine origin. Although several isolates from the marine sources are explored. These agents are cytarabine (AraC), trabectedin, eribulin which is a synthetic derivative.

2.2.1. Cytarabine and nucleoside analogues⁶⁴

Tethya crypta a marine Caribbean sponge was extracted the two bioactive nucleosides such as spongothymidine and spongouridine, discovered by Bergmann and Burke in the early 1950s this led to further exploration of marine environment for the drug discovery. Thus, cytarabine (AraC) a potent antileukemic agent, and the antiviral agent, AraA (adenine arabinoside) were discovered. This further led to the development of various nucleoside analogues showing significant anticancer activity which were developed later.

2.2.2. Clofarabine

In 2004, Clofarabine a second-generation antileukemic agent was approved which has significant safety and efficacy. Used for the treatment of pediatric patients with acute lymphoblastic leukemia, further clinical trials are in process. In addition, its role in the treatment of adult patients

with acute myeloid leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia and the myelodysplastic syndrome has shown positive results.^{65,66}

2.2.3. Sapacitabine (CYC-682)⁶⁷

It is an orally bioavailable nucleoside analogue prodrug. Mechanism of action includes breaking of the single-strand after incorporation into DNA, which are converted into double-strand break at the S phase of cell cycle. It has been shown to be active in the treatment of elderly patients with AML. It received orphan drug designation for the treatment of AML and for the treatment of myelodysplastic syndromes in 2010.

2.2.4. Trabectedin⁶⁸

The structure of ecteinascidin derivatives was isolated and discovered in 1986 however trabectedin the most active of the ecteinascidins, was reported in 1990. 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.

2.2.4.1. Uses . Used in advanced soft-tissue sarcoma and ovarian cancer by the FDA and the EMA.

2.2.4.2. Zalypsis (PM-10450) and lurbinectedin (PM-01183)^{69,70}. They have progressed into clinical trials, and their discovery and development have been discussed. It blocks the oncogenic transcription factor FUS-CHOP and reverses the transcriptional program in myxoid liposarcoma. It reverses the genetic program created by this transcription factor, trabectedin promotes differentiation and reverses the oncogenic phenotype in these cells. Other mechanism of action known are it binds and alkylate DNA at the N2 position of guanine. It is known from in vitro work that this binding occurs in the minor groove, spans approximately three to five bpbases and is most efficient with CGG sequences. Additional binding sequences are TGG, AGC, or GGC. Once bound, this reversible covalent adduct bends DNA toward the major groove, interferes directly with activated transcription, poisons the transcription-coupled nucleotide excision repair complex, promotes degradation of RNA polymerase II, and generates DNA double-strand breaks.

2.2.4.3. Halichondrin B and Eribulin^{71,72}. The segregation and underlying explanation of the intricate regular item, halichondrin B, alongside a few other halichondrin subsidiaries, were first revealed from the marine wipe Halichondriaokadaia in 1986, and firmly followed by reports of the detachment of similar series of mixtures from various wipes gathered in various regions, going from the Central Pacific to the Indian Ocean to waters off New Zealand. It

was displayed to go about as a tubulin-weakening specialist and was supported for preclinical improvement by the US National Cancer Institute in mid 1992. The acquirement of adequate supplies of source crude material end up being testing, however enormous scope assortments and in-ocean hydroponics of the wipe *Lissodendoryx* sp continued off the shoreline of New Zealand as a team with nearby researchers, and adequate amounts of halichondrin B were disengaged for preclinical investigations. In the meantime, quite a while before its endorsement for preclinical turn of investigating the absolute combination of halichondrin B, and, in 1992, they revealed that they had integrated halichondrin B and norhalichondrin B. Working as a team with researchers at the then Eisai Research Institute, the natural not really settled to dwell predominately in the ring piece of the atom, and near 200 subordinates of the shortened regular item were made and assessed. Straight on correlations of unadulterated halichondrin B and the best manufactured analogs, utilizing in vitro time course tests and in vivo concentrates in mice with human xenografts, showed that the shortened halichondrin B simple, presently known as eribulin, with underlying similitudes to halichondrin B showed altogether more intense movement in the in vivo contemplates. This compound was picked for cutting edge preclinical and afterward clinical examinations, utilizing materials made under cGMP conditions by absolute combination. Following broadened clinical preliminaries, eribulin was endorsed for the therapy of headstrong bosom malignancy by the FDA in 2010. The disclosure and improvement of this compound, including the movement from the combination of halichondrin B to the underlying union of eribulin, have been checked. Moreover, papers on the modern strategies that empowered the enormous scope creation of eribulin have been distributed. Until now, eribulin is by a wide margin the most perplexing medication at any point created by absolute blend, and it is a demonstration of the entirety of the specialists in three nations and different associations that coordinated to make it a triumph.

2.3. Anti-cancer agents derived from bacteria and fungi⁷³

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.

2.3.1. Rapamycin^{74–77}

The discovery of rapamycin 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. Initially reported to have antifungal activity, it was approved for use as an immunosuppressive agent (trade name, Rapamune) in 1999. While reported to have antitumor activity in 1984, only reports of the identification of TOR ('target of rapamycin') as the molecular target in yeast in 1991, followed by mTOR as the mammalian homologue in 1994, ultimately led to the development of a wide variety of anticancer and other pharmacologic agents.

Chemical modifications have yielded two clinically approved anticancer drugs.

1. **Everolimus:** It 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 (NCT00790036), liver (NCT01035229), and stomach (NCT00879333) cancers.
2. **Tem sirolimus:** It was first approved 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.
3. **Carfilzomib (Kyprolis™):** It is 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.
Uses: Refractory multiple myeloma who had received prior treatment with bortezomib, thalidomide, or lenalidomide.
4. **Midostaurin:** It is a semisynthetic derivative of staurosporine, an indolocarbazole alkaloid isolated from *Streptomyces staurosporeus*. It is sold under the brand name *Rydapt & Tauritmo* both by Novartis. It works as a multi-targeted protein kinase inhibitor that has been investigated for the treatment of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and advanced systemic mastocytosis. The U.S. Food and Drug Administration (FDA) considers it to be a first-in-class medication.

2.4. Specific target agents

2.4.1. Maytansinoids⁷⁸

Maytansine, a novel macrocyclic compound, was secluded in very low yield in the mid 1960s from the Ethiopian plant, *Maytenus serrata* (Hochst. ex A. Rich.) Wilczek. Derivatives of maitansine are known as maytansinoids. Some are being

explored as the cytotoxic part of counter acting agent drug forms for disease therapy and the immune response drug form trastuzumabemtansine is a supported medication for the therapy of particular sorts of bosom malignancy in the EU and in the US. They have primary comparability to the 'ansa' anti-microbials, for example, the rifamycins; normal item physicists had contemplated whether maytansine was of microbial beginning.

2.4.2. Ansamitocins⁷⁹

In 1977, the seclusion of the firmly related ansamitocins from the bacterium *Actinosynnempretiosum*. The ansamitocins gave a prepared and manageable wellspring of maytansinoids, and the subordinates DM1 and DM4 have been arranged from suitable ansamitocins. Formation with Monoclonal Antibodies DM1 and DM4 have been formed through either thioether or disulfide linkages with different monoclonal antibodies focusing on an assortment of tumors.

T-DM1: Linkage of DM1 to the endorsed her2neu - designated immunizer, trastuzumab, gives T-DM1 or ado-trastuzumabemtansine.

2.4.2.1. *Uses*. It showed huge adequacy in the therapy of patients with cutting edge for metastatic HER2-positive bosom malignancy who had flopped somewhere around two medicines with the at present supported medications, trastuzumab and the tyrosine kinase inhibitor lapatinib.

2.4.3. Brentuximab vedotin⁸⁰

Brentuximab vedotin is framed by formation of monomethyl auristatin E (vedotin), got from dolastatin 10, an optional metabolite initially disengaged from the marine mollusk, *Dolabella auricularia*, yet later segregated from a *Symploca* types of cyanophyte which was demonstrated to be in the eating regimen of the mollusk.

2.4.3.1. *Uses*. CD30-positive lymphoproliferative issues like Hodgkin's lymphoma, EMA in 2011 and 2012, individually. The formation of vedotin or firmly related analogs with antibodies focusing on epitopes found in different tumors, including breast, gastrointestinal, pancreatic, prostate, ovarian and renal malignant growths, leukemias, melanomas and NSCLC are under clinical preliminaries.

2.5. Discovery and evaluation of anti-cancer agents from natural sources⁸¹

From epidemiological studies it was evident that people with diet rich in fruits and vegetables are less prone to cancer and thus the chemotherapeutic agents were studied under clinical trials include β -carotene from carrots, lycopene from tomatoes, indoles from cruciferous vegetables, curcumin from turmeric, catechins from green

tea, and anthocyanins from blueberries. Some clinical trials have failed with variety of agents and active constituents.

2.6. Drugs from natural origin currently in clinical trials⁸²

Other examples of natural product-derived agents in clinical trials include, Polyphenon E Retinoids, soy isoflavones, vitamin C, vitamin D, and vitamin E. In addition, curcumin has failed in clinical trials but its derivatives are still under clinical trials.

2.7. Cancer chemopreventive agents from natural source^{83,84}

A traditionally Taxol and CPT isolation and bioassay has led to discovery of several natural products that are chemopreventive. Similar approach towards the development of anticancer agents has been studied using epigenetic pathways or signaling pathways including Keap1-Nrf2, and the Keap1-Nrf2-ARE signaling pathway and led to the discovery very useful agents.

2.7.1. Repurposing

Using this strategy, the active constituents from dietary natural products, nondietary natural products, semisynthetic derivatives, and known natural products with hitherto unknown mechanism of action. A resounding example of the latter is the quassinoid bruceantin and the close structural relative brusatol have been discovered.

2.7.1.1. Bruceantin . It was originally discovered as a cancer chemotherapeutic agent and dropped due to poor efficacy in advanced-stage cancer patients. It is a potent inducer of cell differentiation and subsequently found to inhibit tumor growth at low doses in the absence of toxicity.⁸⁵

2.7.1.2. Resveratrol . It was isolated from a nonedible legume following bioassay-guided fractionation with inhibition of cyclooxygenase as the objective. It is inhibitor of skin carcinogenesis functioning by a pleiotropic mechanism of action. It is a constituent of grapes and grape wine, thus this industry received substantial importance in past years.⁸⁶

3. Conclusion

The natural products have been used for both chemoprevention and chemotherapeutics. The natural products from terrestrial, marine and microbial sources have been reviewed and discussed in this review. Further anticancer drug evaluation from dietary sources have also been discussed. Farther the vaccine development for cancer excluding some cancers, the natural products have been more affordable and easily available therapies for

cancer. Whether in extract, isolate, synthetic, semisynthetic, improved formulations or as a conjugate, the natural products have served the purpose of life saving and improving the quality of life in many cases.

4. Source of Funding

None.

5. Conflict of Interest

None.

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