# NATURAL DERIVATIVES FOR THE TREATMENT OF BREAST CANCER: A REVIEW

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## ABSTRACT

The primary objective of this review is to explain about active natural compounds for the treatment of cancer. Discovery of Phytochemical based anticancer drug are also explored in last decades. The authors want to broaden the study of phytochemicals, both for their potential as drugs and for their soundness as research subjects. So, for the treatment of breast cancer, knowledge on anticancer phytochemicals is highlighted.

## KEYWORD

Phytochemicals, anticancer, preclinical, clinical, medicinal plants, breast cancer.

## INTRODUCTION

Breast cancer is the main type of cancer that kills women globally. Mortality of patients has increased suffering from breast cancer. Present treatments are adjuvant chemotherapy, surgery, hormone therapies, radiotherapy but there is still no effective heal of breast cancer[1]. Natural products and their derivatives posses characteristics of diverse biologic activities, structural diversity, low toxicity and side effects, and presence of a broad range of sources are important role in the development of novel anticancer drugs. Recent research revealed that dietary phytochemicals can target a number of breast cancer-related pathways, provide a protective feedback against cancer, and play a critical role in preventing breast cancer. This review explains some phytochemicals' potential to combat breast cancer and discusses natural compounds that work against these mechanisms, such as the arachidonic acid pathway, the cell apoptosis pathway, epigenetic modifications, and aromatase activity[3-5]. Some synthetic and phytochemicals can aid in a patient's emotional distress and anxiety as well as lessen the negative side effects of traditional treatment of cancers[5,6]. It has been proven via numerous research that natural substances are beneficial for treating breast cancer. Nature provided anticancer agents of various origin, plant-derived drugs and microbial derived drugs such as Bleomycin, Dactomycin and Doxorubicin[7-12].

**THERE ARE SOME MEDICINAL PLANT WHICH ARE USED IN THE TREATMNENT OF BREAST CANCER:**

- Taxol (paclitaxol)
- Taxotere (dacetaxol)
- Vincristine
- Navelbine(vinorelbine)
- Etoposide
- Teniposide
- Topotecan

**THERE ARE SOME MICROBIAL ORIGIN WHICH ARE USED IN THE TREATMENT OF BREAST CANCER**

- Doxorubicin
- Dactomycin
- Bleomycin

**TAXOL (PACLITAXEL)**

The taxanes are anticancer medicines that generate cytotoxicity by means of a unique mechanism.This has led to the medicine paclitaxel being approved by regulators for application in the palliative management of breast cancer and ovarian cancer and who are resistant to chemotherapy in the United States and many other countries.. The current issue is to create paclitaxel-based treatment plans for malignancies where a cure or enhanced survival may be feasible. In 1971, paclitaxel was discovered to be the extract's active ingredient. Initially, paclitaxel administered on a 24-hour schedule was shown to have significant anticancer effect in women with metastatic breast cancer.Taxel is given on a 24-hour cycle.51,86 25 women with metastatic illness who had only undergone one chemotherapy course,The median period for illness progression was nine months, and 56% of patients showed significant responses.51 This high degree of activity was confirmed by a confirmatory experiment in which paclitaxel (250 mg per square metre) and granulocyte colony-stimulating factor were administered to women who had either had adjuvant therapy alone or no prior therapy; 62 percent of these women experienced substantial responses. Neither the hormonal-receptor status nor previous adjuvant therapy were associated with the likelihood of a substantial response. Responses occurred in both trials in tumours that were blatantly anthracycline-resistant as well as in all sites of metastases.These favourable outcomes with paclitaxel in patients with metastatic breast cancer are equivalent to those seen

in preliminary research on the anthracyclines, one of the most potent treatments for the disease. Determining the role of paclitaxel at increasingly earlier phases of the disease and ultimately in adjuvant therapy will be a part of its further development for the treatment of breast cancer. The Eastern Cooperative Oncology Group is using either paclitaxel, doxorubicin, or both to treat previously untreated women with metastatic breast cancer. The use of paclitaxel-based treatment will be added into adjuvant trials if it shows to be more effective.

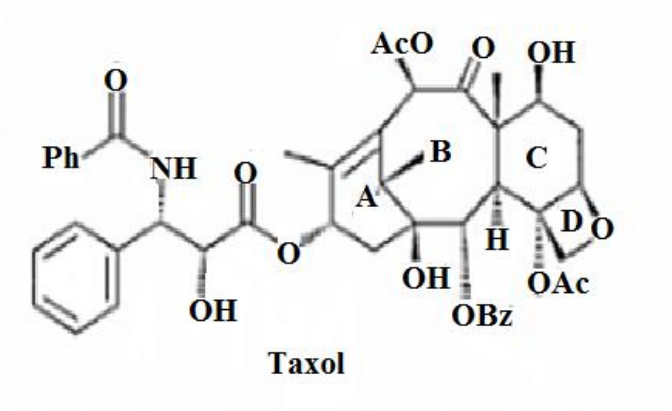



Fig:1 Structure of Taxol

The efficacy of paclitaxel as an adjuvant therapy for high-risk patients is also being investigated in a multicenter trial utilising high, moderate, and low dosages of doxorubicin and cyclophosphamide followed by either paclitaxel and then tamoxifen or simply tamoxifen. Paclitaxel administration and scheduling for women with metastatic breast cancer are being studied. According to preliminary findings of a European trial using three-hour infusions of paclitaxel at 135 or 175 mg per square metre, there are no appreciable differences in response rates (29 percent [high dose] vs. 22 percent [low dose]) or median survival (11.7 months [high dosage] vs. 10.5 months [low dose][13-15].

**Mechanism of Action:**The cancer treatment paclitaxel works by concentrating on microtubules. Structure of Microtubules are cylindrical hollow structures and average diameter is 25–30 nm. Which are in dynamic equilibrium with tubulin heterodimers, which are made up of beta and alpha protein subunits. Microtubules' primary work during cell division is to form the mitotic spindle. they are essential for maintaining cell shape, motility, and cytoplasmic. Microtubules are assembled and tubulin is produced during the G2 and prophases of mitosis. A dynamic equilibrium exists between tubulin subunits contained in microtubules, arranged head to tail, with faster development (plus ends) at one end and

slower growth (minus ends) at the other. Under steady-state conditions, the net tubulin assembly rate equals the net disassembly rate, maintaining the microtubule length constant. The minus ends of microtubules are frequently anchored primarily in the centrosome, whereas the plus ends explore the cytoplasm and interact with cellular structures..Dr. Horwitz discovered that paclitaxel prevents cell division by encouraging the synthesis of stable microtubules and preventing their depolymerization, especially from -tubulin heterodimers. In order to inhibit cell reproduction, exposed cells are subsequently trapped in the G2/M phase of the cell cycle and eventually perish. Paclitaxel selectively and irreversibly binds to the N-terminal 31 amino acids of the beta-tubulin subunit in the microtubules in place of tubulin dimers[16-18].

## TAXOTERE (DACITAXOL)

The treatment for advanced breast cancer hasn't changed all that much in recent years; it still only has palliative goals in mind. The addition of new, active medications is one strategy to improve the efficacy of the treatment. A taxoid derivative known as Taxotere® (docetaxel) was discovered in a European yew., Taxus baccata, needles. Microtubule assembly is aided by taxotere, which also prevents their depolymerization. As first-line chemotherapy, Using Taxotere at 100 mg/m2, 1 hour infusion without typical premedication for hypersensitivity events, one EORTC Clinical Screening Group (CSG) phase II trial showed a significant anti-tumor activity: In 32 patients who could be evaluated for response, there were 5 full and 18 partial replies (72% overall response rate; 95% confidence interval (53%-86%). Additionally, patients undergoing first- and second-line chemotherapy for advanced illness, as well as those who are refractory to anthracycline-containing regimens, are supported by additional studies in this action. The most common side effects were neutropenia in grades III and IV without severe infection and Grades I and II skin toxicity. Fluid retention syndrome, a persistent cumulative and non-life-threatening toxic side effect, has been reported in patients receiving Taxotere.

Researchers are currently looking on ways to reduce fluid retention, such as starting medicine before therapy even begins or lowering the dose to 75 mg/m.

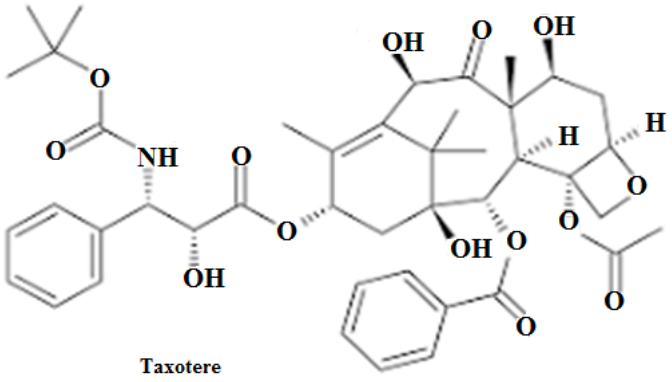



Fig:2 Structure of Taxotere

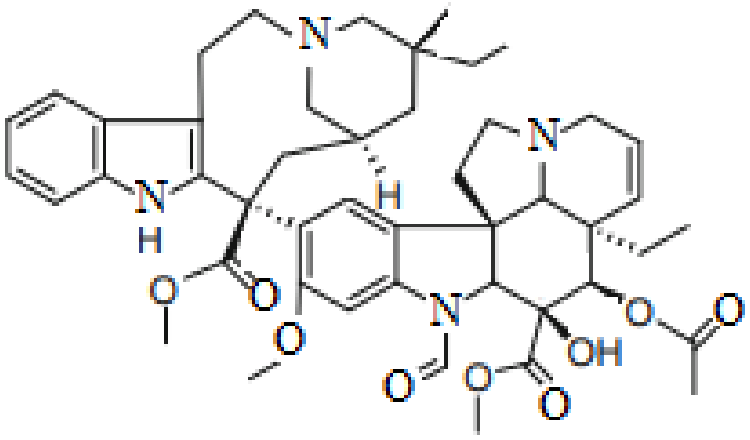
The antineoplastic medications Taxol and Taxotere belong to a new class known as the taxoids. These drugs work by promoting microtubule assembly and inhibiting microtubule depolymerization, which kills cancer cells both in vitro and in vivo.Hypersensitivity reactions initially prevented the clinical development of Taxol, while regular premedication and extended infusion times have helped to reduce these effects. As a result, there has been a lot of interest in similar medicines that could reduce hypersensitivity.[1]

**Mechanism of Action:**A chemotherapeutic medication from the second generation of the taxane family is docetaxel.The primary mechanism of action of docetaxel, a derivative of the original taxane paclitaxel, is binding to beta-tubulin to encourage its proliferation and maintain its conformation. This hinders the normal assembly of microtubules into the during G2/M. Docetaxel also inhibits the expression of the BCL2 gene, which cancer cells commonly overexpress in order to prolong their survival. This gene can be turned off to make cancer cells more susceptible to apoptosis. (Nicole G February 24, 2022.)

## VINCRISTINE

392 patients with advanced cancer participated in a series of dose-level studies on vincristine. In a sizable percentage of individuals with advanced reticulum cell sarcoma, breast cancer, bladder cancer, Hodgkin's disease, and carcinomas of unclear source location, it caused tumour regressions. At 25 jug/kg/week, responses happened about as frequently as at larger

dosages. In contrast to patients who experienced only mild or no toxic effects or those who experienced severe pharmacological effects on normal tissues, individuals who experienced moderate toxicity had the highest response rates. Central nervous system dysfunctions and dose-related sensory, motor, and anomie neuropathy were seen. Thrombocytopenia and leukopenia were noted. The patients' good- or poor-risk status affected the frequency of responses attained and the length of those responses. When prognostication and actual survival times were compared, it was found that the prediction of survival was rather accurate. Responders outlived non-responders by a longer margin. The survival extension in breast cancer patients beyond prognosis cannot be attributed simply to vincristine-induced remission period. In several other disorders, vincristine's therapeutic response was able to counteract a dismal prognosis and, it appears, increase survival above what was anticipated..




(Holland and Scharlau 1 June 1973)[2]

Fig:3 Structure of vincristine

**Mechanism of Action :**The tubulin-binding chemicals, like vincristine and other vinca alkaloids, which derive their biological features from impairing microtubule activity, are part of the class of mitotic poisons. Tubulin heterodimers make up the polymeric fibres known as microtubules. Tubulin's - and -subunits combine to form dimers, and vincristine's binding site is found on the -subunit at the intersection of two heterodimers (fig. ). Thus, the only tubulin-binding substances identified to date that do not absolutely bind one tubulin heterodimer are vincristine and other vinca alkaloids. This crucial quality is essential to the distinctive mode of action of vinca alkaloids. Large doses of the chemicals have a specific ability to break the microtubule filaments. The vinca alkaloid then causes the fibres to unite and remain attached to one another. Such disordered, frequently spiralled fibres are unable to carry out the mitotic spindle's crucial function of separating the chromatids during mitosis. Vinca alkaloids, which stabilise microtubule dynamics by binding to the terminals of microtubule filaments, also slightly impair this function.

Vincristine can also with combination of other drugs like:

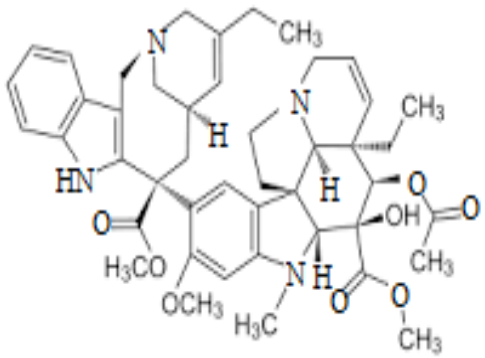
- Vincristine in combination with cyclophosphamide, doxorubicin, and prednison
- Combination of Vincristine with Methotrexate
- Vincristine combined with dacarbazine or procarbazine (Škubník J 2021 Aug 31.)[3]

**NAVELBINE(VINORELBINE)**

A semi-synthetic vinca alkaloid called vinorelbine tartrate prevents microtubule assembly. The catharanthine and vindoline-containing dimeric molecules that make up the vinca alkaloids are catharanthine and vindoline. The catharanthine nucleus is where vinorelbine undergoes structural change. By interacting with tubulin, vinca alkaloids appear to exert their anticancer effect, which stops mitosis at metaphase. Thevinca alkaloids interact with tubulin in qualitatively distinct ways, according to in vitro research.As a result, vinorelbine depolymerizes mitotic microtubules more effectively than axonal microtubules.6 Clinically, axonal microtubule activity is linked to neurotoxicity, whereas mitotic microtubule activity is connected with anticancer activity. As a result, vinorelbine has an advantage over the other vinca alkaloids, especially in terms of neurotoxicity. Vinorelbine is eliminated in three steps, with a terminal phase half-life of between 28 and 44 hours.2 Vinorelbine is mostly eliminated through the liver, while urine elimination rates as high as 18% have been seen.2 Although it has not been determined how renal or hepatic impairment affect vinorelbine distribution, dose reductions are necessary in patients with hepatic impairment.For a total bilirubin of 2.1-3.0

[3]

mg/dL, a dose reduction of 50% is advised, and a dose reduction of 75% is advised for a total bilirubin of 3.0 mg/dL or above. Renal insufficiency does not need changing the dosage. For both intravenous and oral vinorelbine, Variol et al. showed equivalent pharmacokinetic and pharmacodynamic correlations. Vinorelbine has been linked to a number of different medication interactions. First, when coupled with mitomycin, vinorelbine and other vinca alkaloids have been linked to acute pulmonary responses. Secondly, granulocytopenia is more common when vinorelbine and cisplatin are used together than when vinorelbine is used alone. Finally, individuals receiving vinorelbine and paclitaxel sequentially or in combination should be watched for neuropathy symptoms and signs. When docetaxel was given before vinorelbine, Airoldi et al. reported a pharmacokinetic interaction and asubstantial change in neutrophil nadir count.




**NAVELBINE**

Fig:4 Structure of Navelbine

Vinorelbine, a Single-Agent First-Line Therapy for Metastatic Breast Cancer, In phase II investigations of first-line, single-agent vinorelbine at 30 mg/m2/week, conducted in the late 1980s and early 1990s, response rates varied from 35% to 52%. Which included 157 patients with metastatic breast cancer, Fumoleau et al[20].

**ETOPOSIDE**

High-dose etoposide (1,500-2,500 mg/nr) was administered to 23 patients with advanced breast cancer who had already had treatment. With a median response time of 5 months, objective regression was seen in six out of 23 patients (or 26% of the total). Except for the bone, every location exhibited responses. Response was dose-dependent, with 2/23 responses at 1,500 mg/m2 compared to 11/23 measurable lesion responses at 2,000 mg/nr. The treatment plan could be carried out on an outpatient basis with just normal supportive

measures. Patients with advanced breast cancer may eventually get high-dose etoposide as part of combination chemotherapy therapies.Early in the 1970s, etoposide (VP 16, 4'-dimethyl-epipodophyllotoxin BD-ethylidene glucoside), one of the derivatives of podophyllotoxin, was used for the first time in cancer clinical trials. Etoposide has been shown to be both a powerful single agent and an essential component of combination therapy for a number of human malignancies. Despite the fact that certain early studies in breast cancer were not encouraging, we reconsidered the use of high-dose etoposide as a single drug in patients with advanced refractory breast cancer[21]. Now, etoposide is frequently used in high-dose chemotherapy regimens.

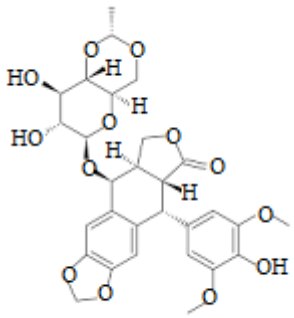



**Fig:5 Structure of Etoposide**

**A Derivative with a Novel Mechanism of Action: Etoposide**

**Different from Podophyllotoxin's mechanism:**Etoposide stops cells from entering during mitosis, in contrast to podophyllotoxin, which blocks cell replication in metaphase at mitosis. Because of this, it prevents cell development in the early G2 phase, which serves as an arrest point, and the late S phase, which is when DNA replication takes place. Therefore, VP-16 and VM-26 are phase-specific cytotoxic drugs. An increase of cells in the G2 phase has also been observed during in vivo investigations. The fact that VP-16 can cause a cycle stoppage in metaphase at mitosis, but only at extremely high concentrations that are incompatible with those encountered in vivo, is interesting to note. Therefore, despite having comparable behaviours, etoposide and teniposide work through different mechanisms than podophyllotoxin. Etoposide has also been shown to impede the assembly of microtubules and to not bind to tubulin. Teniposide and Etoposide inhibit nucleoside transport, metabolism, and incorporation into DNA, similarly to podophyllotoxin.

**Etoposide Acts on DNA**

We made substantial progress in our knowledge of the mechanism of action of etoposide when Like and Horwitz found DNA breakage in HeLa cells after exposure to VP-16 and VM-26 at low concentrations (1 M). The cause of this was later shown to be dose-dependent single-stranded DNA breakage. The study also showed that a C-4 structure promoted DNA breakdown and that it required a free 4'-phenol. When the medicine was stopped, the cell then repaired these DNA damage.

**Involvement of an Enzyme in the Mechanism of Action**

The effects of VP-16 and VM-26 on DNA protein crosslinks, single-stranded DNA breaks, and double-stranded DNA breaks were shown by Wozniak and Ross in 1983. They also discovered that while DNA breaking could be seen in isolated nuclei, it could not be generated on purified DNA. Therefore, it was believed that a nuclear enzyme was responsible for creating these double-stranded DNA breaks. Their findings made it possible to link DNA breaks to medication cytotoxicity. Finally, etoposide and teniposide's targets for action were discovered by Long and Minocha and Ross et al. virtually simultaneously as a result of all these observations.Topoisomerase II has already been linked to the mechanism of action of intercalative medications such anthracyclines and acridines, which stabilise the cleavage complex between topoisomerase II and its DNA substrate. Etoposide, despite not being a DNA intercalating agent, functions similarly to DNA and topoisomerase. (Philippe Meresse Number 18, 2004)[4]

**TENIPOSIDE**

A semi-synthetic podophyllotoxin derivative known as teniposide (VM-26) has significant antitumor effect against cancers of the testicles, small cell lung cancer, acute leukaemia, and malignant lymphomas. The efficacy in the majority of other solid tumours is either modest or has not yet undergone enough testing. We present results of a phase II teniposide study in individuals with advanced breast cancer who had not had any prior treatment. Previous studies utilising daily or weekly schedules of teniposide demonstrated minimal activity in individuals with metastatic breast cancer who had undergone extensive pretreatment. In more recent investigations, 52 patients who had previously had chemotherapy showed an overall response rate of 8% PRs using a regimen of days 1 through 5 every three weeks. Accordingly, 383 patients who had received a lot of pretreatment had a 7% response rate to etoposide (VP-16). The two epipodophyllotoxins' limited activity has been seen at doses that cause moderate to severe hematologic damage. However, when teniposide was employed as a

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second-line or later treatment for lung cancer, important therapeutic effects were missed. There has only been one phase II trial of epipodophyllotoxin derivatives in breast cancer patients who had not previously received treatment [10]. Etoposide 230 mg/m2 day 1-3 every four weeks was utilised as a treatment. A 15% response rate was seen (3 PRs out of 20 patients), however the toxic side effects, particularly hematologic ones, were minimal because no dose reductions were required. In our study, the median response time was 9 months, and the response rate was 37% (95% confidence limits 19%-58%). However, we were willing to accept a proportionally greater hematopoietic toxicity. The WBC and platelet nadirs showed a wide range of variance. Similar toxicity has been found by other writers [11]. Age, tumour load, or performance status were the only variables we could not identify that predicted the haematological damage. These findings imply that teniposide has at least modest effect in elderly patients with advanced breast cancer who have received prior endocrine therapy, despite the fact that the patient population in this trial was carefully chosen based on age and sites of metastatic illness (soft tissue being predominate).. (D. Nielsen n.d.)[5]

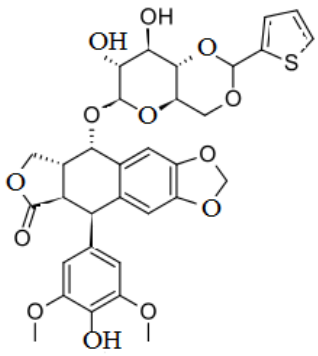


Fig:6 Structure of Teniposide

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**MECHANISM OF ACTION:** Epipodophyllotoxin teniposide is linked to etoposide both structurally and pharmacologically.2 DNA strands can break into single and double strands as a result of teniposide's inhibition of type II topoisomerase. It doesn't strongly attach to DNA or intercalate into it. Teniposide prevents cells from going through mitosis by stopping cell growth in the late S2 or early G2 phases of the cell cycle. (St. Laurent 1 July 2014).

**MICROBIAL ORIGINS**

**DOXORUBICIN**

The most effective chemotherapeutic agent now used to treat breast cancer is doxorubicin (DXR), a member of the anthracycline class. However, it has been demonstrated that DXR can cause medication resistance and even cancer growth, which results in a poor prognosis and survival rate for patients. (Claudia Christowitz 1 August 2019)

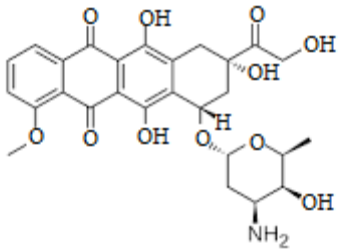


Fig:7 Structure of DOXORUBICIN

**MACHANISM OF ACTION**:In cancer cells, doxorubicin is hypothesised to function by two separate mechanisms: (i) intercalation into DNA and disruption of topoisomerase-II-mediated DNA repair; and (ii) generation of free radicals and damage to cellular membranes, DNA, and proteins. When doxorubicin is oxidised to semiquinone, an unstable metabolite that is then converted back into doxorubicin, reactive oxygen species are created. In addition to initiating the apoptotic pathways that lead to cell death, reactive oxygen species can damage membranes, lipids, DNA, and cause oxidative stress, lipid peroxidation, and oxidative stress. Among the possible genes that may have an impact on this pathway are the free radical-deactivating genes (glutathione peroxidase, catalase, and superoxide dismutase) and the oxidation reaction-capable genes (NADH dehydrogenases, nitric oxide synthases, and xanthine oxidase). Alternatively, doxorubicin, which likewise damages DNA and kills cells, can poison topoisomerase-II as it enters the nucleus. Potential pharmacogenes for this region of the system include the enzymes TOP2A, MLH1, MSH2, TP53, and ERCC2 that are involved in DNA repair pathways and cell cycle control. Others are included based on results from model systems, although even though the evidence for some of them (TOP2A) is

undisputed, the polymorphic nature of these candidate genes may be worthwhile to examine in PGx research. (Caroline F. Thorn 2012 Jul 1.)

**Dactinomycin:** Dactinomycin is an injectable antineoplastic antibiotic used to treat choriocarcinoma in adult women as well as solid tumours in children. Dactinomycin can cause serious liver damage in large dosages, including sinusoidal obstruction syndrome.

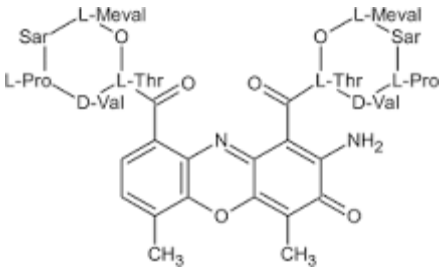


Fig:8 Structure of Dactinomycin

**Mechanism of Action**: The Actinomycin Dactinomycin is one. Dactinomycin functions as a protein synthesis inhibitor as well as a nucleic acid synthesis inhibitor.

**Bleomycin**

Bleomycin was initially extracted from culture broth of the fungus Streptomyces verticillus that was found in dirt at a Japanese coalmine and was discovered in 1966 by Umezawa and colleagues. It is a group of at least 13 tiny, 1500 Da molecular weight, water-soluble glycopeptidic antibiotics. The names of the glycopeptides are A1-6, A0-2, and B1-6. At least 80% of the clinical combination is composed of the fractions A2 and B2. The bleomycinic acid, a distinctive structural element shared by all bleomycins, is their single structurally distinct feature (61). Bleomycin's capacity to generate single- and double-strand DNA breaks in mammalian cells is what makes it cytotoxic. Iron, copper, and cobalt are just a few of the metals that bleomycin is effective in chelating. The most active complex is the bleomycin-Fe2-complex. Complexes like Cu2, Co2, and Ru2 are only active under a relatively narrow range of circumstances. Bleomycin has the highest affinity for cobalt of all the metals, and their chelation is permanent[22].

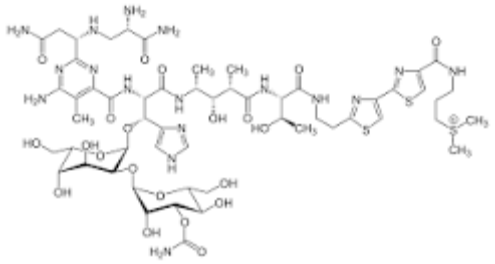

Fig:9 Structure of Bleomycin

**Mechanism of action:** Bleomycin's cytotoxicity is mostly caused by direct DNA damage. Chromosome gaps, deletions, and DNA fragmentation are all signs of single- and doublestrand DNA breaks caused by bleomycin. In order to damage DNA, bleomycin needs oxygen and metals as cofactors (67). Cu2 and bleomycin combine to produce a complex, which the cell then absorbs. The bleomycin-Cu2 combination is thought to be a prodrug that, once inside the cell, transforms into the physiologically active Fe2-bleomycin.When the Fe2-bleomycin-complex binds to O2 and then to DNA, the quaternary complex (Fe2-bleomycin-O2-DNA) induces DNA cleavage. Fe2-bleomycin attaches to O2 quite quickly, and DNA aids in maintaining the stability of the complex. The interaction with the DNA at the minor groove has a definite nucleotide selectivity, such as a predilection for GC base pairs. The chromatin is cut by bleomycin at the level of the DNA that connects nucleosomes. With roughly 6–10 single strand breaks to 1 double strand break, bleomycin causes both single and double strand DNA breaks. The initial cleavage is more sequence specific than the attack on the opposing strand. The first cleavage site is within one nucleotide of where it is cleaved. Bleomycin, also is considered to have an 8–10 piece DNA severing capacity per molecule, and 3 106 molecules of the medication can sever about 5 106 double strands of DNA in a single cell. It has been shown that 30 seconds after bleomycin enters the cell, DNA fragmentation takes place very swiftly. Bleomycin also produces free nucleic bases without strand breaking, degrades oxidised RNA, targets small chemical compounds, and induces lipid peroxidation, all of which could be detrimental to cells.One of two mechanisms by which bleomycin kills cells. If only a few bleomycin molecules are present, the cell is stopped in the G2-M phase, enlarges, and polynuclei and micronuclei can be detected. Bleomycin does this by causing the distinctive DNA fragmentation that short-circuits the apoptosis pathway. Cell shrinkage, membrane blebbing, and chromatin condensation follow this. (Anita Gothelf October 2003)[17].

**CONCLUSION:**

Natural compounds with microbial and plant origins are employed in the therapy and management of breast cancer. These natural derivatives are used as single or combined chemotherapeutic treatments for breast cancer. The majority of the world's applications for natural products derived from plants and microorganisms are widespread, and they have been used for a very long period. The importance of research projects to improve these derivatives' ability to treat patients with breast cancer must be increased. They don't have any unusual harmful effects and can still function through routes. This review discusses the significance of natural derivatives with microbial and plant origins as well as their mechanisms of action. More extensive research is therefore required to confirm the appropriate operation of these derivatives, which will enable us to better comprehend their therapeutic applications and resolve the issues related to breast cancer.

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