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Anti-Cancer Drugs-Common Types in Libya Tamoxifen: Structure and Synthesis

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Abstract

This research reviews the role of anticancer organic compounds, focusing on Tamoxifen as a Selective Estrogen Receptor Modulator (SERM) and briefly comparing it to Vincristine and Vinblastine (Vinca alkaloids). First, the review includes the classification of cancer stages, revealing the symptoms of each stage. Moreover, the review provides an overview of the general classification of most cancer drugs, types of cancer drugs used specifically in Libya, their structural differences and pharmacological mechanisms, their mechanism of action, metabolism, and pharmacokinetics, their manufacturing/extraction and methods of synthesis (descriptive/industrial level), an explanation of their effects on cells and tissues, their possible or probable side effects, and a guideline on monitoring imported food products containing preservatives that may interact with cancer drugs or affect public health, and emphasizes the importance of monitoring their expiry dates and ensuring legal compliance for all related activities. The research also focuses on cancer types of interest, with particular emphasis on the most prevalent types in Libya (such as breast, colon, lung cancer, colorectum, and other types). The research also provides an idea of the total number of all cancer patients in Libya, comparing the data for both sexes up to the year 2020 according to previously published articles by the National Cancer Control Program (NCCP) and National Cancer Registry.

Keywords: Anticancer Drugs, Breast, Vinka Alkaloids, Tamoxifen, Colon, Lung

INTRODUCTION

Cancer is a broad term for a group of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. There are more than 100 different types of cancer affecting humans, classified according to the tissue or organ of origin – such as breast, lung, colon, prostate, liver, and skin cancer [1].

Stages of Cancer

According to the American Cancer Society [2], cancer staging should follow the TNM classification of cancer stage, where 'T', 'N', and 'M' stand for Tumor, lymph nodes, and Metastasis, respectively.

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Chemical Treatment of Cancer

Organic compounds play a major role in anticancer drug design. Tamoxifen is a selective estrogen receptor modulator (SERM). It is used mainly in estrogen-positive breast cancer. Here, an example is provided of how organic molecules can inhibit tumor growth. A comparison is also made between Tamoxifen, Vincristine, and Vinblastine, outlining their mechanisms, reactions, and structural differences.

In Libya, the most common cancer types based on the National Cancer Registry data include breast

cancer (most common among females), followed by colorectal and uterine cancers. Among males, lung, colon, and prostate cancers are most prevalent [3]. For this reason, this research focuses on breast, colorectal, and lung cancer as the primary target areas for anticancer drug application.

Globally, several anticancer drugs are widely used, such as Tamoxifen, Doxorubicin, Paclitaxel, Cisplatin, Vincristine, and Vinblastine [4]. In Libya, the treatment protocols often include Tamoxifen for breast cancer, Vincristine/Vinblastine for hematologic cancers, and Cisplatin for solid tumors [5] (Figures 1–3).

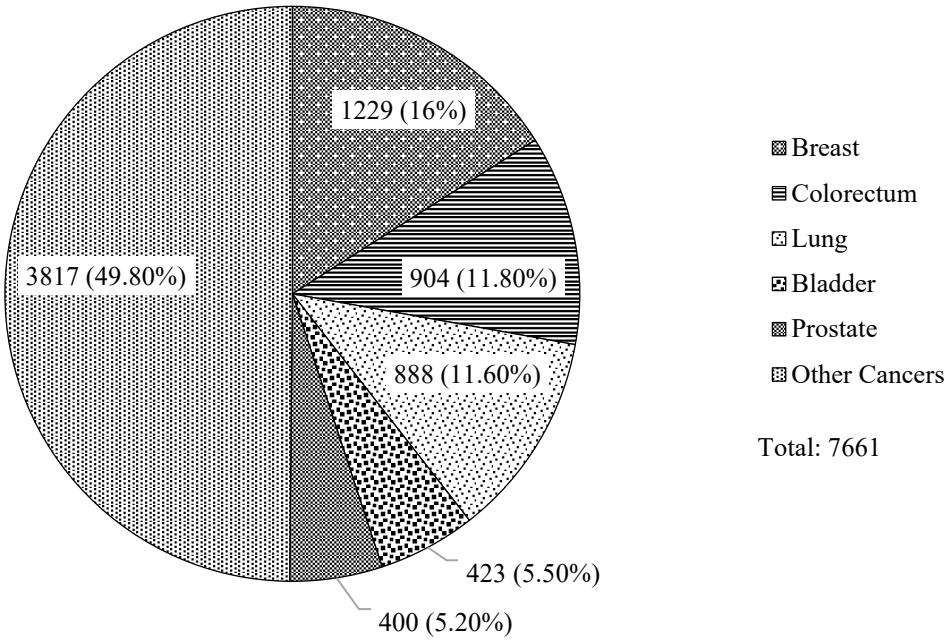


Figure 1. Number of new cases in 2020, both sexes, all ages [18, 19].

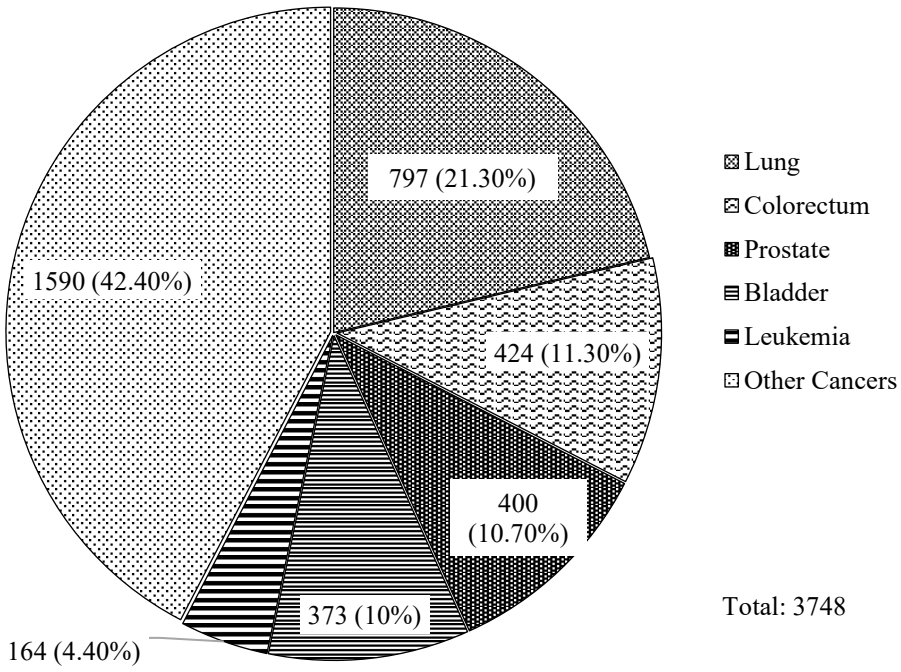


Figure 2. Number of new cases, males, of all ages [18, 19].

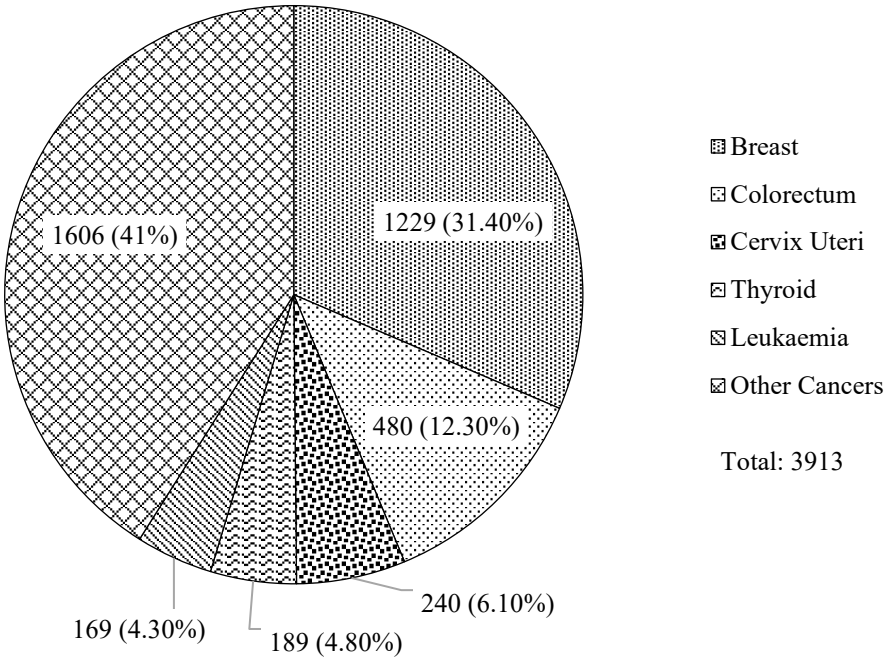


Figure 3. Number of new cases, females, of all ages [18, 19].

Anticancer drugs are classified into several main groups, including:

1. Alkylating agents
2. Antimetabolites
3. Antitumor antibiotics
4. Plant alkaloids [6]
5. Hormonal agents
6. Enzyme inhibitors
7. Monoclonal antibodies
8. Immunomodulators
9. Platinum-based compounds
10. Kinase inhibitors
11. Topoisomerase inhibitors
12. Retinoids
13. Proteasome inhibitors
14. Histone deacetylase inhibitors
15. PARP inhibitors
16. Antibody-Drug Conjugates

Among these, the three most commonly used drugs in Libya are Tamoxifen, Vincristine, and Vinblastine, due to their wide availability and effectiveness in treating breast, lung, and colon cancers.

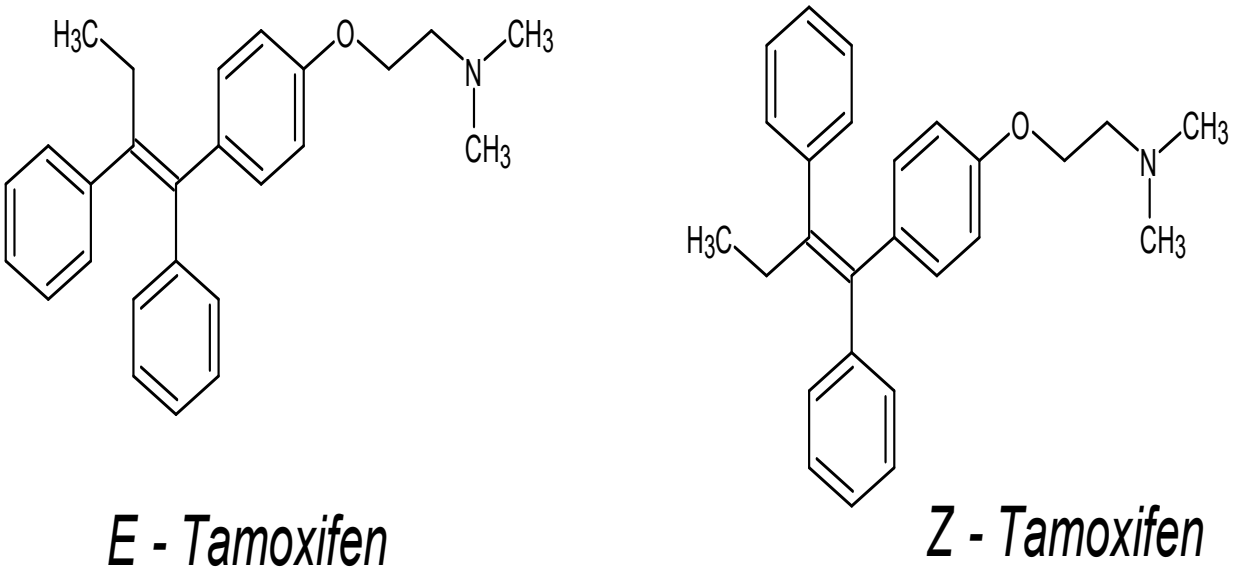
Tamoxifen Overview

- *Formula:* $C_{26}H_{29}NO$
- *Group:* Non-steroidal triphenylethylene derivative.
- *Function:* Selective Estrogen Receptor Modulator (SERM).
- Binds to estrogen receptors and blocks estrogen effects in breast tissue.
- Metabolized to 4-hydroxytamoxifen (active form).
- *Common Cancers:* Breast cancer, lung cancer, colorectal cancer, prostate cancer, and gastrointestinal cancers.

As a priority in our review, we will focus specifically on breast, colorectal, and lung cancer due to their importance and local prevalence. In Libya, the National Registry Data and local studies showed that breast cancer is the most common cancer among females, followed by colorectal and uterine cancers, while among males, lung, colon, and prostate cancers are the most common. For this reason, we have chosen to focus on breast, colorectal, and lung cancer as the primary areas of focus for drug application [18].

Tamoxifen Structure

- Triphenyl groups, all attached to ethylene.
- Two ether linkages (–O–)
- Dimethylamino side chain (–$N(CH_3)_2$)
- Flat aromatic system High receptor binding affinity
- Include structural illustration in the slide showing the three phenyl rings and the dimethylaminoethyl side chain attached through the ether linkage to highlight the chemical configuration [7].



E- Tamoxifen is prescribed under the name Novadex (Tamoxifen citrate) For women with ductal carcinoma in situ (DCIS) and women at high risk for breast cancer [10].

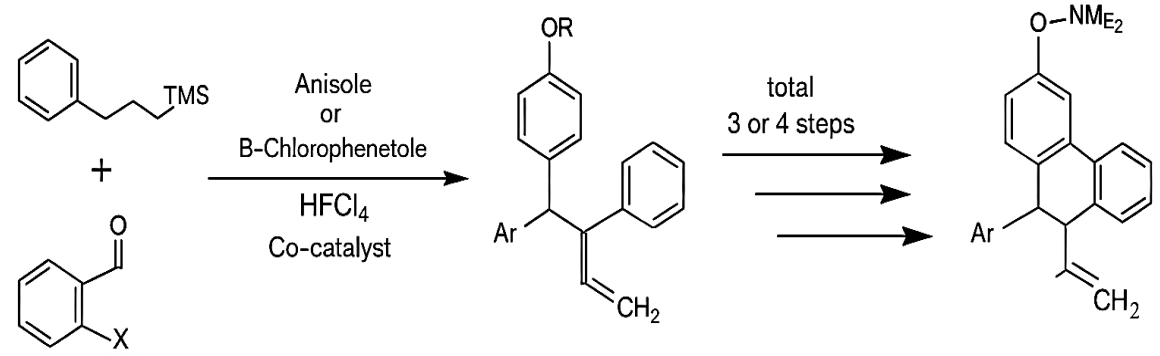
Synthetic pathways of tamoxifen

Many researchers succeeded in synthesizing tamoxifen [20].

1. Start with a triphenylethylene backbone precursor.
2. Use a Grignard reagent to add phenyl groups via nucleophilic addition to a ketone.
3. Employ the Wittig reaction to introduce ethylenic linkage between phenyl rings.
4. Functionalize the molecule through dimethylamino-ethyl substitution to form the side chain responsible for estrogen receptor affinity [20, 24].

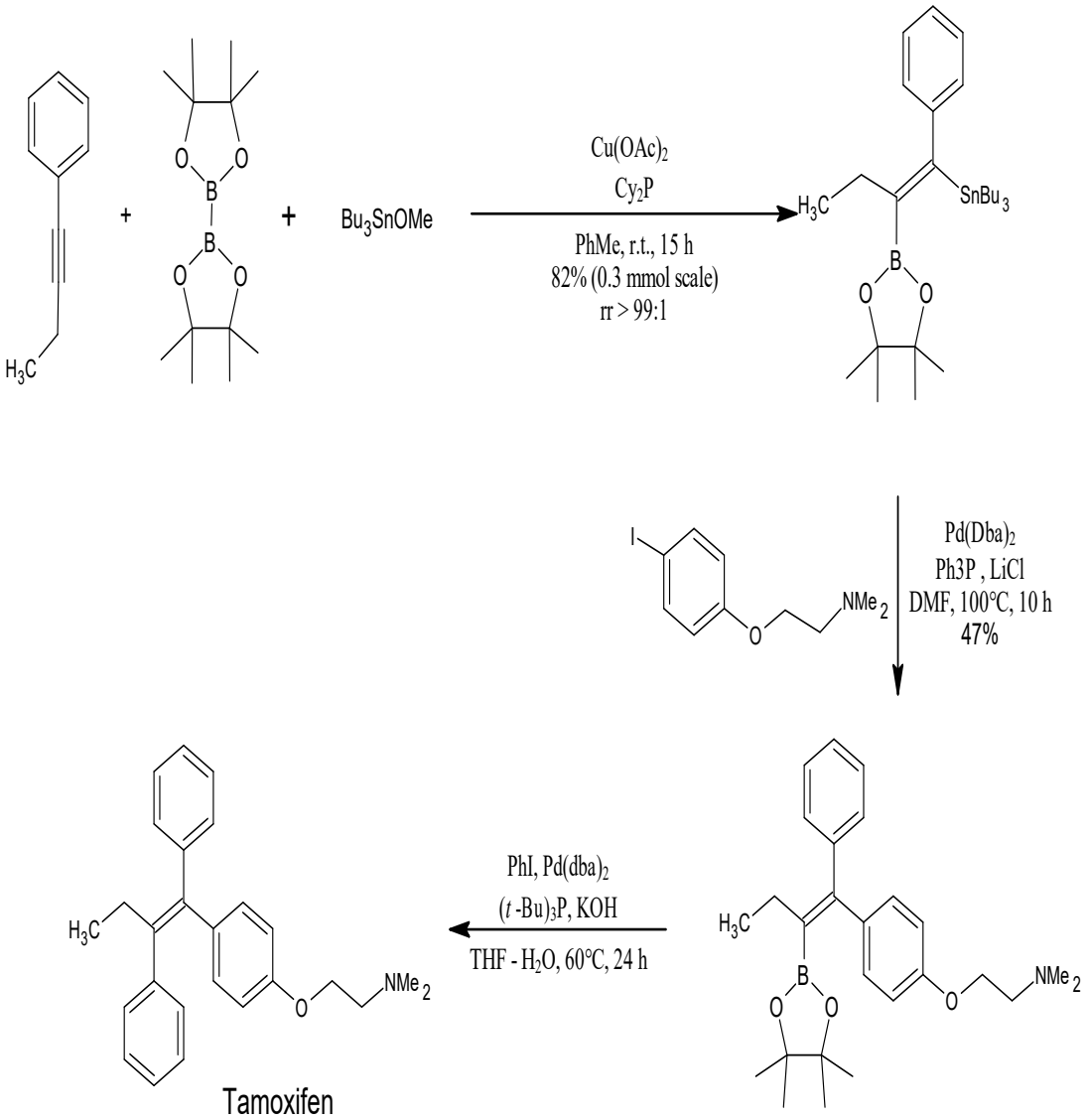
A second approach involves two new synthetic pathways:

1. The aldol reaction of benzyl phenyl ketone with acetaldehyde followed by Friedel–Crafts substitution with anisole in the presence of $Cl_2Si(OTf)_2$ to produce 1,1,2-triaryl-3-acetoxybutane, a precursor of the tamoxifen derivatives.
2. The second one utilized the novel three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and aromatic nucleophiles using $HfCl_4$ as a Lewis acid catalyst to produce 3,4,4-triarylbutene, that is also a valuable intermediate of the tamoxifen derivatives (Scheme 1) [17].



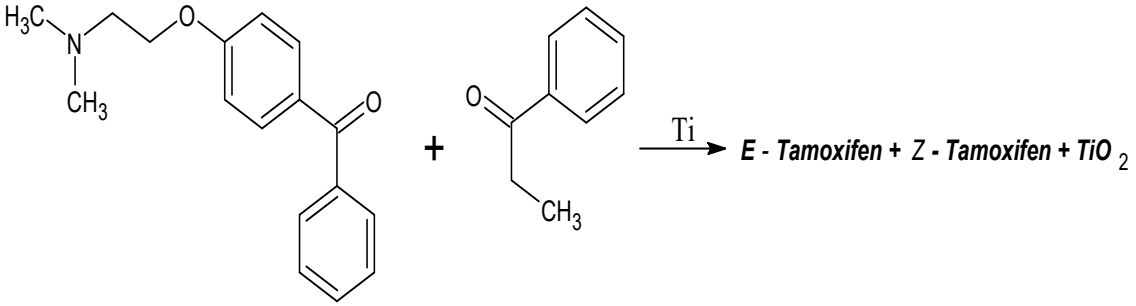
Scheme 1. Synthesis of Tamoxifen from aromatic aldehydes, cinnamyltrimethylsilane.

A third approach includes sequential addition of phenyl rings on ethylphenyl acetylene through catalytic steps using protection groups (Scheme 2) [22].



Scheme 2. Synthesis of Tamoxifen from acetylene derivatives.

Also, a low valent titanium was used in the coupling reaction (Scheme 3) [23].



Scheme 3. Synthesis of Tamoxifen isomers using titanium

Pharmacokinetics of Tamoxifen

- *Absorption:* Tamoxifen is administered orally and is well absorbed from the gastrointestinal tract.
- *Distribution:* It is distributed to adipose tissue and target tissues (such as breast tissue) and binds to plasma proteins.
- *Metabolism:* It undergoes extensive hepatic metabolism via CYP enzymes (particularly CYP2D6 and CYP3A4) to active metabolites such as 4-hydroxy-tamoxifen and endoxifen, which have a higher affinity for estrogen receptors.
- *Excretion:* Its metabolites are largely excreted via bile and feces.

These aspects affect pharmacodynamics, individual response, and drug interactions (e.g., drugs that inhibit CYP2D6 reduce the generation of active metabolites) [11].

Mechanism of Action of Tamoxifen

According to the National Institute of Health, tamoxifen's mechanism of action is a dual process where it acts as a selective estrogen receptor modulator (SERM), meaning it blocks estrogen in some tissues, such as breast tissue, while acting like estrogen in others, like bone. Briefly, in breast, tamoxifen

- Competes with estrogen for receptor binding.
- Inhibits estrogen-induced DNA synthesis and cell proliferation.
- Acts as antagonist in breast tissue and as partial agonist in bone and uterus.
- Prevents cancer cell division and induces apoptosis.
- It blocks estrogen receptors (ERα, ERβ) by occupying the ligand-binding site, causing conformational change and recruitment of co-repressors instead of co-activators, thus inhibiting transcription of estrogen-responsive genes that promote proliferation [8].

Explanation of the Effects of Tamoxifen Used on Cells/Tissues (Practical Illustration):

- *Effect on Breast Tissue:* Tamoxifen prevents estrogen from binding to its receptors in breast cells, thus reducing the activity of growth signaling pathways and decreasing cell entry into the S phase (DNA synthesis), thereby reducing cell division.
- *Effect on Cancer Cells:* It increases apoptosis signals in estrogen-dependent cells.
- *Side Effects on Other Tissues:* Due to its activity as a stimulant in the endometrium, it increases the risk of uterine cancer and some hematological effects (risk of thrombosis).

Metabolic Reactions of Tamoxifen

In Liver (CYP Enzymes):

- Tamoxifen → 4-Hydroxytamoxifen (CYP2D6) → N-Desmethyl-tamoxifen (CYP3A4)
- Active metabolites show higher estrogen receptor affinity [3].

Major Side Effects of Tamoxifen

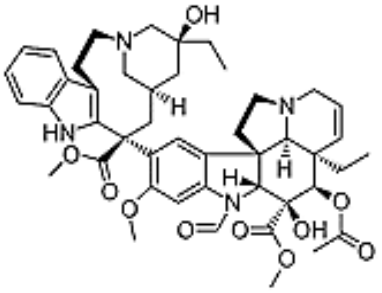
Tamoxifen side effects may include [25].

- Menopause-like symptoms, including hot flashes, night sweats and vaginal dryness
- Weight gain (more common) or fluid retention (edema)
- Irregular or loss of menstrual periods
- Leg swelling
- Nausea
- Vaginal discharge
- Skin rash
- Erectile dysfunction
- Fatigue
- Headaches

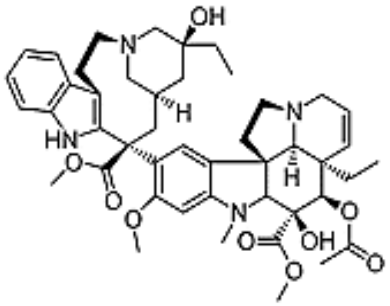
Critical Interactions and Precautions
- Drugs that inhibit CYP2D6 may reduce endoxifen synthesis, thus affecting treatment efficacy.
- Therapeutic monitoring and CYP2D6 genotype considerations may be beneficial in some cases.

Vincristine & Vinblastine Overview [14, 15]
- Both are Vinca alkaloids derived from Catharanthus roseus [6, 7, 9].
- Used in leukemia, lymphoma, Hodgkin's disease, etc.
- Mechanism: Inhibit microtubule formation → block mitosis

Studies demonstrated the potent antileukemic effects of vinblastine, the prototype of vinca alkaloids, leading to its development as a promising chemotherapeutic agent against cancer. The vinca-site family of MDAs has since exhibited clinical success in the treatment of hematologic malignancies, lymphatic neoplasms, and solid tumors, including breast cancer, NSCLC, and small-cell lung cancer (SCLC) [12].



A. Vincristine



B. Vinblastine

Vincristine (Oncovin)
- *Formula:* $C_{46}H_{56}N_4O_{10}$• Contains an aldehyde group (–CHO)
- Causes neurotoxicity (nerve damage) at high doses
- Less bone marrow suppression than Vinblastine

Vinblastine (Velbe)
- *Formula:* $C_{46}H_{58}N_4O$
- Contains a methyl group ($–CH_3$) instead of aldehyde.
- Causes more bone marrow suppression.
- Less neurotoxic than Vincristine

Mechanism of Action (Vinca alkaloids) [13]
- Bind to tubulin → inhibit microtubule polymerization.
- Prevent formation of mitotic spindle.
- Arrest cells in metaphase → apoptosis.
- Reaction representation

Tubulin + Drug ⇌ Tubulin–Drug Complex → ⟹ Cell division stops → Apoptosis (Programmed Cell Death)

Chemical Mechanism (Simplified)
1. $C_{46}H_{58}N_4O_9$ (Vinblastine) + Tubulin → Vinblastine–Tubulin Complex
2. Prevents elongation of microtubules [12].
3. Mitotic spindle fails to form.
4. Cell cycle arrest (M-phase).
5. Apoptosis initiated

Combination Therapy
- Vincristine or Vinblastine is often used with Tamoxifen.
- Tamoxifen reduces estrogenic stimulation.
- Vinca alkaloids inhibit cell division.
- Synergistic anticancer effect.

Combination therapy aims to attack cancer through multiple pathways — hormonal inhibition (Tamoxifen) and mitotic arrest (Vinca alkaloids), thus reducing resistance and enhancing tumor cell apoptosis [9].

Resistance Mechanisms
- Increased P-glycoprotein (drug efflux).
- Mutation of tubulin structure.
- Enzymatic alteration of Tamoxifen metabolism.
- Reduced receptor binding efficiency.

Toxicities
- *Tamoxifen:* Endometrial cancer, thrombo embolism.
- *Vincristine:* Peripheral neuropathy.
- *Vinblastine:* Bone marrow suppression, nausea

Future Directions
- Development of Tamoxifen analogs with reduced side effects.
- Nano-drug delivery systems to target tumors directly.
- Study of vincristine/vinblastine derivatives with enhanced selectivity.

Recommendations

To reduce cancer incidence, especially among young adults, the following are recommended:
1. Promote early screening and awareness programs.
2. Reduce exposure to carcinogenic chemicals and preservatives.

3. Encourage healthy diet and physical activity.
4. Increase research on genetic factors and early-onset cancers.
5. Establish national policies to control imported substances that may affect cancer risk [10].

CONCLUSION

- Organic compounds like Tamoxifen and Vinca alkaloids remain key anticancer drugs.
- Structural modifications improve their therapeutic potential.
- Understanding mechanisms helps design next-generation anticancer agents.
- Emphasis on chemical synthesis and mechanism provides insight for targeted therapy.

Despite increasing awareness of survivorship issues and the resilience of cancer survivors, many challenges remain. These include a fractured health care system, poor integration of survivorship care between oncology and primary care settings, clinician workforce shortages, lack of diversity in the medical workforce, knowledge gaps about the needs of cancer survivors, and lack of strong evidence-based guidelines for posttreatment care. These challenges are exacerbated by financial and other barriers to quality care, particularly for communities of color and low-income and rural neighborhoods, who continue to experience substantial gaps in early detection and access to high-quality treatment. To address these disparities and further progress in cancer survivorship, ongoing efforts to identify best practices for the equitable delivery of quality cancer treatment, rehabilitation and posttreatment cancer care are needed.

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