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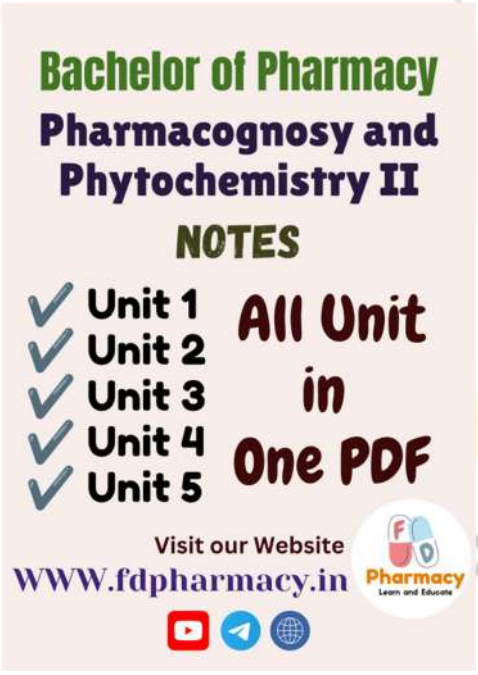
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# MEDICINAL CHEMISTRY - II

## UNIT 1

TOPIC :

- **Plant products :** Etoposide, Vinblastinsulphate, Vincristin sulphate

# Plant Products as Antineoplastic Agents

Plant-derived compounds, also known as phytochemicals, are important anticancer agents. They can inhibit or prevent the growth of cancer cells by interfering with processes such as cell division, DNA replication, and tumor blood supply.

### Advantages

- Often fewer side effects compared to synthetic drugs.
- Target rapidly dividing cancer cells effectively.

### Drugs to study

- Vinblastine sulfate
- Vincristine sulfate
- Etoposideo

## Mechanism of Action

Plant-derived antineoplastic agents work through multiple mechanisms:

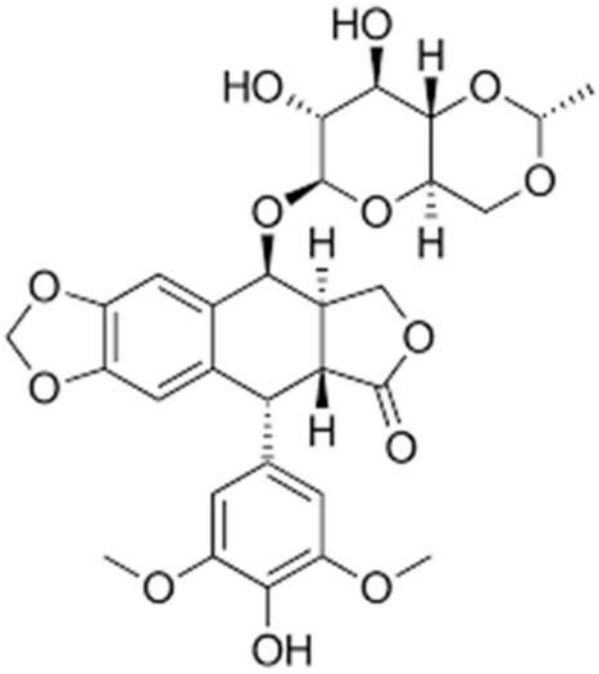
1. Microtubule Inhibition
    - Vinblastine and Vincristine inhibit tubulin polymerization into microtubules.
    - This disrupts mitotic spindle formation, blocking cell division and leading to cell cycle arrest.
2. Topoisomerase II Inhibition
    - Etoposide inhibits topoisomerase II, an enzyme crucial for DNA unwinding and repair.
    - Inhibition causes DNA strand breakage, preventing replication and transcription, which induces apoptosis.

# Etoposide

- Etoposide is a semisynthetic derivative of podophyllotoxin, classified as a topoisomerase II inhibitor.
- It is used as a cytotoxic chemotherapeutic agent for lung cancer, testicular cancer, lymphomas, and leukemias.
- Administered intravenously or orally, with oral bioavailability ~50%.

## Chemical Structure

- IUPAC Name: 4′-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside]
- Molecular Formula: $C_{29}H_{32}O_{13}$
- Molecular Weight: 588.56 g/mol
- Structure




## Mechanism of Action

- Topoisomerase II Inhibition:
  - Etoposide binds to DNA-topoisomerase II complex → prevents religation of DNA strands after cleavage.
- DNA Damage:
  - Accumulation of double-stranded DNA breaks → triggers apoptosis in rapidly dividing cells.
- Cell Cycle Effect:
  - S and G2-phase specific, affecting DNA replication and repair.
- Cytotoxicity:
  - Leads to cell death due to DNA damage and failed repair.

## Synthesis of Etoposide

1. Starting Material:
    - Podophyllotoxin, a natural lignan obtained from Podophyllum
    - +species (roots/rhizomes).
2. Chemical Modifications:
    - Epimerization at C4'
    - Glycosylation at C9 with glucose derivative
    - Protecting group strategies to enhance solubility and stability
3. Purification:
    - Chromatography to obtain clinical-grade etoposide.

## Uses

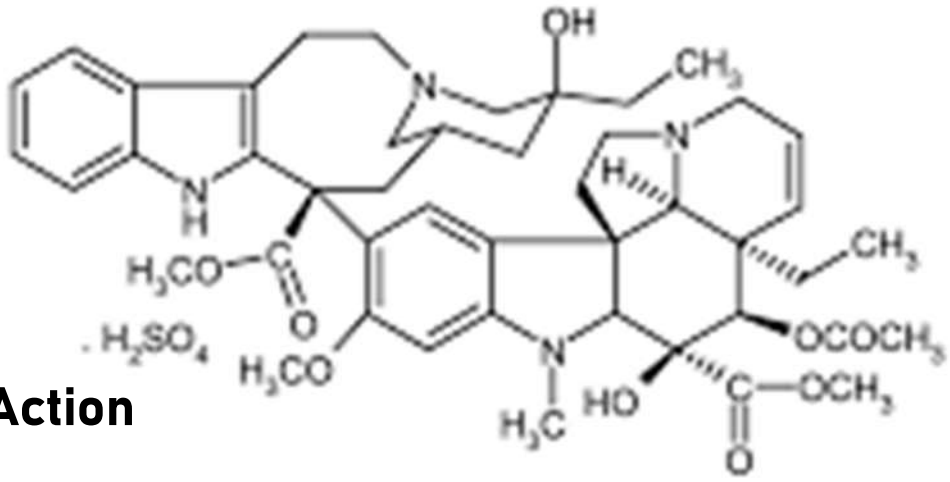
1. Solid tumors:
    - Small cell lung cancer, testicular cancer, ovarian cancer.
2. Hematologic malignancies:
    - Lymphomas, acute leukemias.
3. Combination therapy:
    - Frequently used in combination regimens (e.g., BEP, EP).
4. Side Effects:
    - Myelosuppression (dose-limiting), alopecia, nausea, vomiting, hypotension (IV), and risk of secondary leukemia with prolonged use.

# Vinblastine Sulphate

- Vinblastine is a Vinca alkaloid, a natural antineoplastic agent derived from the leaves of Catharanthus roseus (Madagascar periwinkle).
- Vinblastine Sulphate is the sulfate salt form, used clinically for better solubility.
- Used in Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, breast cancer, and Kaposi's sarcoma.
- Administered intravenously, as oral absorption is negligible.

## Chemical Structure

- Molecular Formula: $C_{66}H_{81}N_4O_{16}\cdot H_2SO_4$
- Molecular Weight: 884.02 g/mol (free base ~810.96 g/mol)
- Structure




## Mechanism of Action

- Microtubule Inhibition:
  - Vinblastine binds to tubulin dimers, preventing their polymerization into microtubules.
- Mitotic Arrest:
  - Disruption of microtubules → arrests cells in metaphase → prevents chromosome segregation.
- Cell Cycle Effect:
  - M-phase specific, targeting rapidly dividing cells during mitosis.
- Cytotoxicity:
  - Leads to apoptosis due to failed mitosis and chromosomal missegregation.

## Synthesis of Vinblastine

1. Source:
    - Naturally derived from Catharanthus roseus leaves.
2. Extraction:
    - Isolation of vindoline and catharanthine alkaloids.
3. Coupling Reaction:
    - Enzymatic or chemical coupling of vindoline and catharanthine → forms vinblastine.
4. Formation of Sulphate Salt:
    - Reaction with sulfuric acid → vinblastine sulphate.

## Uses

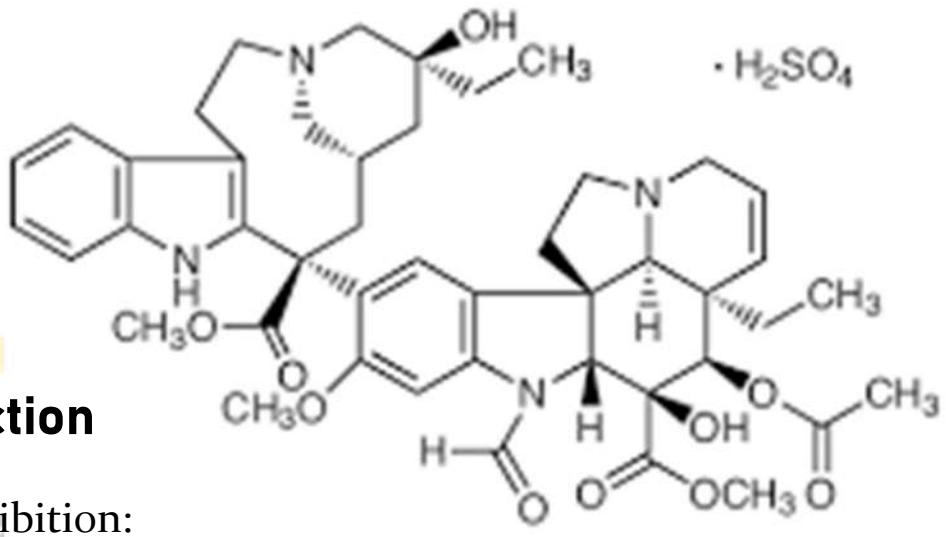
1. Hematologic malignancies:
    - Hodgkin's lymphoma, non-Hodgkin's lymphoma.
2. Solid tumors:
    - Testicular cancer, breast cancer, Kaposi's sarcoma.
3. Side Effects:
    - Myelosuppression (dose-limiting), alopecia, nausea, vomiting, neurotoxicity (less severe than vincristine), and constipation.

# Vincristine Sulphate

- Vincristine is a Vinca alkaloid, a natural anticancer agent derived from the leaves of Catharanthus roseus (Madagascar periwinkle).
- Vincristine Sulphate is the sulfate salt form for better solubility and clinical use.
- Used in acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, neuroblastoma, and Wilms' tumor.
- Administered intravenously, as oral absorption is negligible.

## Chemical Structure

- Molecular Formula: $C_{46}H_{56}N_4O_{10}\cdot H_2SO_4$
- Molecular Weight: 923.04 g/mol (free base ~824.98 g/mol)
- Structure




## Mechanism of Action

- Microtubule Inhibition:
  - Vincristine binds to tubulin dimers, preventing their polymerization into microtubules.
- Mitotic Arrest:
  - Disruption of microtubules → arrests cells in metaphase → prevents chromosome segregation.
- Cell Cycle Effect:
  - M-phase specific, targeting rapidly dividing cells during mitosis.
- Cytotoxicity:
  - Leads to apoptosis due to failed mitosis and chromosomal missegregation.

## Synthesis

1. Source:
    - Naturally derived from Catharanthus roseus leaves.
2. Extraction:
    - Isolation of vindoline and catharanthine alkaloids.
3. Coupling Reaction:
    - Enzymatic or chemical coupling of vindoline and catharanthine → forms vincristine.
4. Formation of Sulphate Salt:
    - Reaction with sulfuric acid → vincristine sulphate.

## Uses

1. Hematologic malignancies:
    - Acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma, non-Hodgkin's lymphoma.
2. Solid tumors:
    - Neuroblastoma, Wilms' tumor, rhabdomyosarcoma.
3. Side Effects:
    - Neurotoxicity (peripheral neuropathy, constipation), alopecia, mild myelosuppression, SIADH, and rarely hepatotoxicity.