WELCOME

TO

This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site http://www.fdspharmacy.in/

You tube https://www.youtube.com/c/FDSpharmacy

Telegram https://t.me/Fdspharmacy

App https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy

E-mail fdspharmacyinfo@gmail.com

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**:

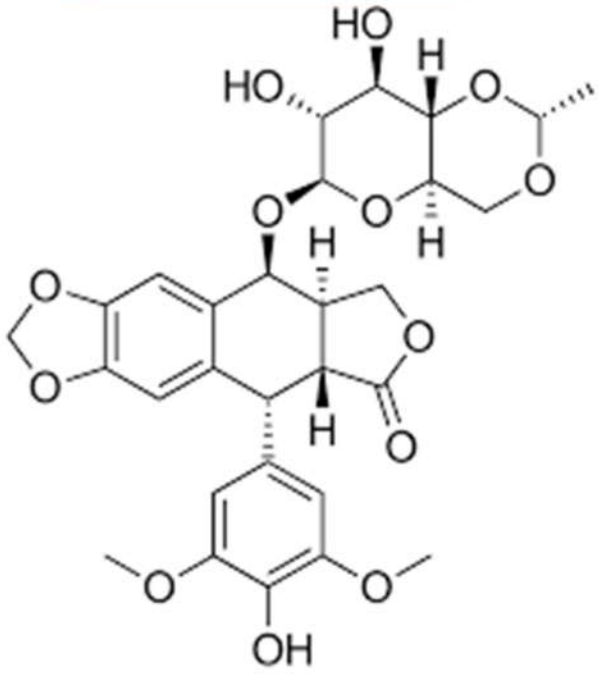
1. **Microtubule Inhibition**
    - **Vinblastine and Vincristine** inhibit **tubulin polymerization into microtubules**.
    - This **disrupts mitotic spindle formation**, blocking **cell division** and leading to **cell cycle arrest**.
2. **Topoisomerase II Inhibition**
    - **Etoposide** inhibits **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

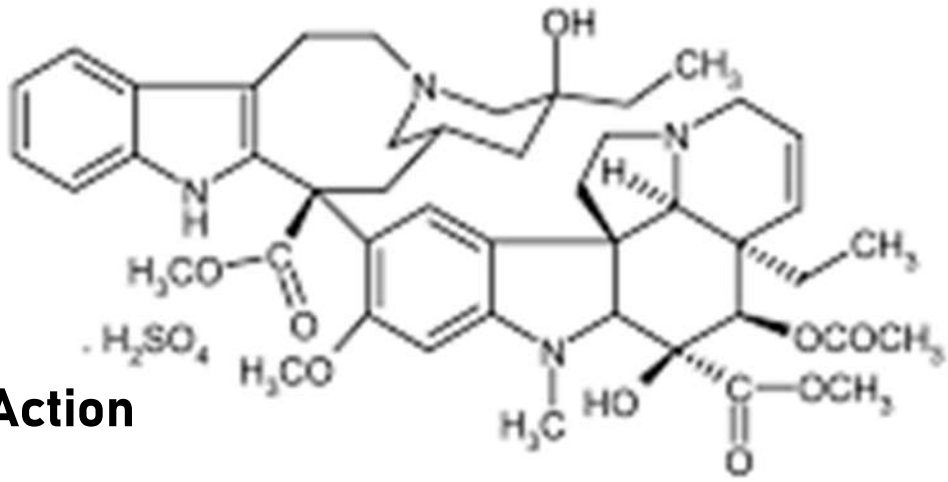
1. **Solid tumors:**
   - Small cell lung cancer, testicular cancer, ovarian cancer.
2. **Hematologic malignancies:**
   - Lymphomas, acute leukemias.
3. **Combination therapy:**
   - Frequently used in **combination regimens** (e.g., BEP, EP).
4. **Side Effects:**
   - Myelosuppression (dose-limiting), 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

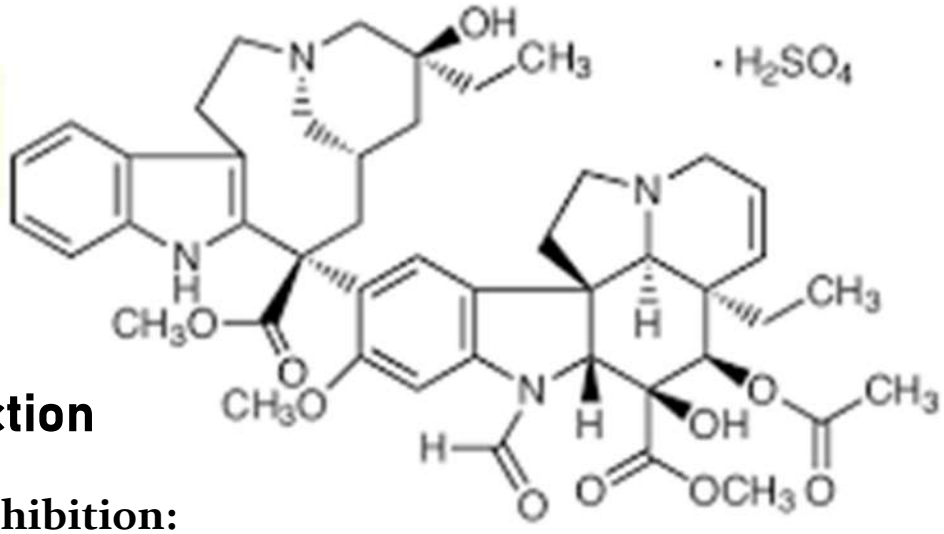
1. **Hematologic malignancies:**
   - Hodgkin's lymphoma, non-Hodgkin's lymphoma.
2. **Solid tumors:**
   - Testicular cancer, breast cancer, Kaposi's sarcoma.
3. **Side Effects:**
   - Myelosuppression (dose-limiting), alopecia, nausea, vomiting, neurotoxicity (less severe than vincristine), and constipation.

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.