Faculty of Pharmacy

Phytotherapy for Cardiovascular disorders and Cancer

Phytotherapy

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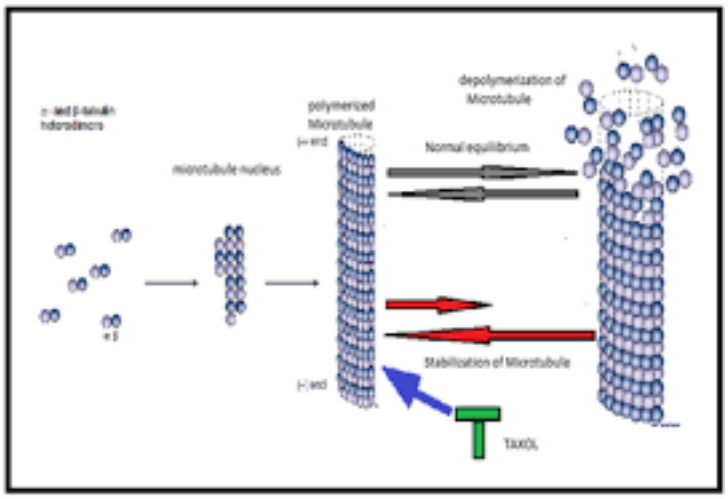

Cardiovascular system (CV)

- Cardiovascular disorders are responsible for many deaths all over the world
- Cardiovascular disorders are a consequence of life style and diet.
- Serious conditions such as heart failure should be treated under supervision of a physician, but some minor forms of CV respond to change in diet and taking more exercise, as well as phytotherapy.

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Foxglove(Digitalis)
كف الثعلب

- *Digitalis purpurea* and *Digitalis lanata* (family: Plantaginaceae): the leaves contain the active glycosides.
- This plant is native to Europe.
- The plant contains cardenolides which are glycosides of steroidal structure.
- The important ones are digitoxigenin, gitoxigenin and gitaloxigenin.

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Digoxin

- Digoxin increases the force of myocardial contraction and reduces conductivity within the atrioventricular node.
- It is used mainly for CHF and is given in a one daily dose in a range of 62.5-250 µg.
- The glycosides have a positive inotropic effect.
- These glycosides have a small therapeutic window.

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Digitalis

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Digoxin

- **Loading dose.**
- **Maintenance dose.**
- **Dose measurement.**
- **Toxicity.**
- **Drug interactions.**
- **Toxic symptoms: nausea, vomiting , anorexia, headache.**

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Loading Dose

- A loading dose is one that is larger than the standard dose:
  - It is given at the beginning of drug therapy to quickly raise the blood level of the drug into therapeutic range.
  - It is used when the desired therapeutic response is required more quickly than can be achieved with the standard dose.

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Maintenance Dose

- A maintenance dose is one that continues to keep the drug in the desired therapeutic range:
  - It is used after a loading dose.
  - For many drugs, patients receive the maintenance dose both at the start of therapy and throughout therapy.

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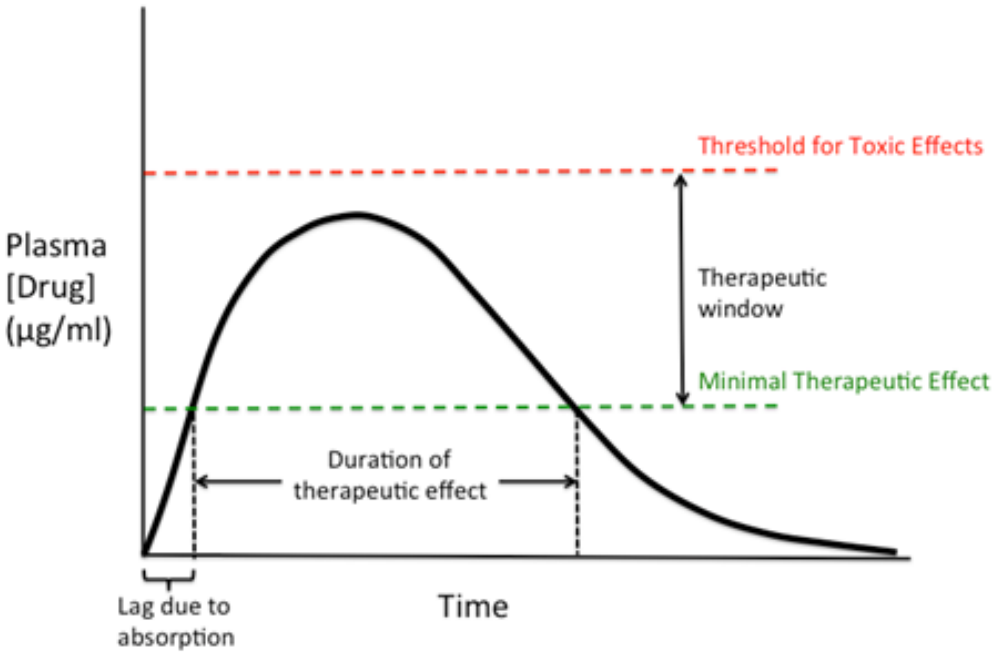
Time Course of Drug Action (Oral)



Four variables are used to calculate the loading dose:

C_p = desired peak concentration of drug

V_d = volume of distribution of drug in body

F = bioavailability

S = salt fraction

The required loading dose may then be calculated as

$$\text{Loading dose} = \frac{C_p V_d}{FS}$$

S = Salt factor

- Percentage (or fraction) of total dose which is active drug (0-100%).

F = Bioavailability

- Percent (or fraction) of a dose that enters circulation (0-100%)
  ---->Of the dose you gave, how much actually gets absorbed = Bioavailability (F).

Cp: Plasma drug concentration at any time

Volume of Distribution of a Drug (V_d):

- THE BIGGER THE V_d THE MORE DISTRIBUTED THE DRUG IS AND VICE VERSA
  -->Volume of compartment necessary to account for total amount of drug in body if present throughout entire body in same concentration as plasma.

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Drug Toxicity

❖**DRUG TOXICITY/ADR/ADE** is defined as "manifestations of the adverse effects of drugs administered therapeutically or in the course of diagnostic techniques. It does not include accidental or intentional poisoning..."

❖It may result when :
- ➢the dose is too high
- ➢the liver or kidneys are unable to remove the drug from the bloodstream

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Side effects:

▪Unwanted effects of a drug seen with **therapeutic doses,** unavoidable.

e.g. Codeine for cough – constipation

Toxic effects :

▪Unwanted effects either due to **over dosage or chronic** use of a drug.

e.g. Streptomycin – Renal damage

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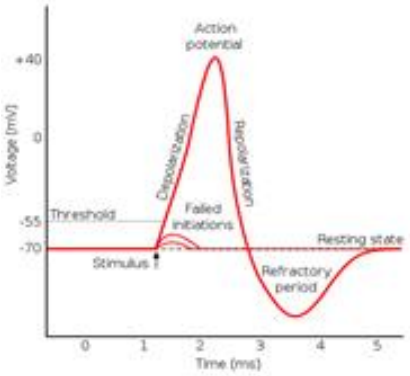
Reasons of digitalis toxicity:

1. Admisnstration of larger maintenance dose.
2. Too rapid digitalisation.
3. Presence of other drugs like: amiodarone, verapamil, quinidine, erythromycine.
4. Hypokalemia.
5. Hypercalcemia.
6. Hypomagnesia.



Digoxin Toxicity

- ***Narrow window between therapeutic and toxic concentrations***
- ***Clinical picture:***
  - Headache, Generalized malaise
  - Nausea and vomiting
  - Altered color perception, halo vision
  - More serious than these are ***digitalis-related arrhythmias.***
- ***Bradycardias*** related to a markedly enhanced vagal effect (e.g., *sinus bradycardia or arrest, AV node block*)
- ***Tachyarrhythmias*** that may be caused by delayed afterdepolarization mediated triggered activity (e.g., *atrial, junctional, and ventricular tachycardia*) most common **paroxysmal atrial tachycardia with block**

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Common digoxin-drug interactions:

❖ **With quinidine:**

- **Quinidine increases digoxin concentration by:**

1. Displacement from plasma proteins.
2. Inhibition of digoxin renal clearance.

❖ **With diuretics (such as anthraquinones, e.g. Senna):**

- Increased digoxin toxicity due to electrolyte imbalance such as hypokalemia.

❖ **With amiodarone: increased toxicity by:**

- Decreased clearance by amiodarone.
- Additive effect.

❖ **With verapamil: increased toxicity by:**

- Decreased renal and non-renal clearance.
- Additive effect.

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Venous insufficiency and circulatory disorders

- Improvements in circulatory disorders arise from a number of different pharmacological effects, particularly those involving anti-inflammatory and anti-oxidant activity.
- The plants which have these properties are important for treatment of hemorrhoids, varicose veins, impaired visual acuity and even enhancement of memory.
- The most important plants are:

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Bilberry (blue berry)

- *Vaccinium myrtillus:* عنبية ، عنب الأحراج
- Widely cultivated in Europe, Asia and North America.
- The fruits ripen from July to September.
- Both the ripe fruit and the leaves are used medicinally.

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Blue berry

- The fruit contains **anthocyanin** glycosides.
- It is **used** for retinopathy caused by diabetes or hypertension.
- The plant has also an anti-oxidant and anti-atherosclerotic effect with anti-platelet effect.

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Ginkgo biloba

- It is useful for peripheral arterial diseases and other circulatory diseases.
- It has complex effects on isolated blood vessels.
- The **ginkgolides** are specific platelet-activating factor antagonist.
- The usual dose

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Ginkgo biloba

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Horse chestnut

- *Aesculus hippocastnum:*
- The leaves are rich in **saponin glycosides**.
- The main one is **aescin**.
- Also, it contains **sterols** and other **triterpenes**,
- **It is useful for:**

1. Chronic venous insufficiency.
2. Bruising كدمات and sport injuries.
3. Deep vein thrombosis.
4. Varicose veins.
5. Prevents edema.

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Horse chestnut

- Also, it is used widely in cosmetics.
- Dose is 600 mg of extract daily which contains 100 mg aescin.

❖ Red vine leaves:

- Certain varieties of grape vine produce red leaves used in treatment of CVI and varicose veins.

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Anti-platelet and anti-atherosclerosis

- Thrombosis and atherosclerosis are a result of lifestyle and high sugar and fat consumption.

❖ **Garlic:**

- It contains a large number of sulphur components which are responsible for its effect.
- The main compound is alliin, which inhibits LDL oxidation {{ Oxidized LDL can produce inflammation in arteries that supply blood to your organs and other tissues, thus promoting atherosclerosis and increasing your risk of having a heart attack or stroke}}.
- Caution should be taken when used with other cardiovascular drugs.

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Anticancer natural products

- Plants have been regarded the basis of sophisticated medical systems for thousands of years.
- WHO has estimated that 80% of the Earth's inhabitants rely on traditional medicine for primary health care.
- The most comprehensive study conducted on cytotoxic agents from nature has been carried out by NCI , a US government agency.

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Anticancer drugs

1- Campetothecine:

- Obtained from the Chinese tree ***Camptotheca acuminata***, family Nyssaceae.

- This alkaloid showed broad spectrum activity as **anticancer** but its toxicity is too high.

- The natural 10-hydroxy camptothecin is more active and is used in China for neck and head cancer.

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Anticancer drugs

- The **synthetic** analogues are **9-aminocamptothecin.**

- Particularly, water-soluble derivatives **topotecan**, **irinotecan** showed good response in number of cancers.

- They are available now for the treatment of ovarian cancer and colorectal cancer, while belotecan (camtobell® = available in USA) is available for small cell lung cancer and ovarian cancer.

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Camptothecin

Mode of action:

- Irinotecan is an antineoplastic enzyme inhibitor primarily used in the treatment of colorectal cancer.
- It is a derivative of camptothecin.
- It inhibits the action of topoisomerase I.

  Irinotecan prevents relegation ابعاد of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death.

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Camptothecin

Side effect of irinotecan:

- Diarrhea , anemia , hair loss, abdominal cramps, vomiting and nausea (common almost to all chemotherapy).

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Anticancer drugs

2. Podophyllum:

- Podophyllum **resin** is obtained from **rhizomes** or roots of *Podophyllum peltatum* (American podophyllum) or *Podophyllum emodi* (Indian podophyllum).

  F. Berberidaceae.
- It is known as May apple.

Constituents:

- It contains 3.5 - 6% of **resin**.
- The active principle is the **lignans**, these include podophylloloxin 20%, α-peltatin 10%, and β-Peltatin 5%.

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Podophyllum

- **Etoposide** is a lignan derivative obtained semi-synthetically from podophylotoxin and is **used for treatment of small-cell lung cancer, testicular cancer as well as lymphomas and leukemias.**
- Teniposide is also used for brain cancer

❖ {{ The **lignans** are a group of chemical compounds found in plants. Plant lignans are polyphenolic substances derived from **phenylalanine** via dimerization of substituted cinnamic alcohols.

❖ **Lignin** is a class of complex organic polymers that form important structural materials in the support tissues of vascular plants and some algae. Lignins are particularly important in the formation of cell walls, especially in wood and bark, because they lend rigidity and do not rot easily. Chemically, lignins are cross-linked **phenolic** polymers.}}

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Anticancer drugs

- **3. Vinicristine and vinblastine:**
- These are obtained from *Catharanthus roseus* (Vinca rosea) which is a Madagascar plant (**Madagascar periwinkle**.
- Now, it is widely cultivated.
- It was used in folklore medicine for diabetes in Europe for centuries and had a reputation as a magic plant.
- The alkaloids in this plant are referred to as Vinca alkaloids.

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Vinca alkaloids

- A screening programme at the pharmaceutical company Eli Lilly revealed that extracts inhibited growth of certain types of cancer cells.
- Bioassay–guided isolation of extracts of the plant led to the finding of these 2 alkaloids.
- Problem with this plant that the content is extremely low.

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Vincristine & Vinblastine

- The generic name for it is **Oncovine** (Eli Lily)
- Used for acute leukemia, Hodgkin's disease and other lymphomas.
- **Vinblastine**: the other drug which is used for Hodgkin's disease, lymphomas, advanced testicular and breast cancer.
- The generic name (Vilban).
- **Mode of action:** it inhibits mitosis by binding to tubulin dimers preventing spindle formation.

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Taxol

- Obtained from ***Taxus brevifolia*** tree.(bark of the stem).
- Collected from USA on the Pacific ocean. The mature tree is 100 years old.
- The plant yield is very **small** 12 kg of bark yield 0.5 gm of taxol.
- It is active for **solid tumors**, **leukemia** and **melanoma cell** line.
- {{ **An abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors.** }}

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Taxol

- **To over come the problem of the low yield:**

1. By conversion of the high yield of the other compound (10-deacetylbaccatin III) in the European species ***Taxus baccata*** into taxo

2. Also, by tissue culture.

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Taxol

- Taxol was marketed by Bristol Myers Squibb for **ovarian cancer**, **breast cancer** and **non-small cell lung cancer.**

- **Mode of action:** prevents the mitotic spindle from being broken down by stabilizing microtubules bundles (prevents depolymerization or disassembly).

- Docetaxel is more water soluble drug than taxol.

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Anthracyclines & Actinomycins

❖These include the antibiotic drugs related to tetracyclines, (**daunorubicin**, **doxorubicin**, and **idarubicin**).

❖**The second group includes the actinomycins: include:**

- Dactinomycin.
- The bleomycins:

1. Bleomycin A2.
2. Bleomycin B2.

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Marine anticancer drugs

- Marines have no history of medicinal use, but with relatively small numbers of these products have been reported.
- There is now one compound in use:
- Aplidine® (**the trade name of plitidepsin**) for colon, bladder, lung, prostate and stomach cancers.
- Plitidepsin is a cyclic depsipeptide [is a molecule that has both peptide and ester linkages in proximity in the same amino acid-containing small molecule or chain].....

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….. isolated from the marine tunicate *Aplidium albicans*.

➢Plitidepsin displays a broad spectrum of antitumor activities, inducing apoptosis by triggering mitochondrial cytochrome *c* release.

Mechanism of Action:

- **Aplidine** inhibits the growth and induces apoptosis in MOLT-4 cells through the indirect inhibition of VEGF secretion which blocks the VEGF/VEGFR-1 autocrine loop necessary for the growth of these cells.

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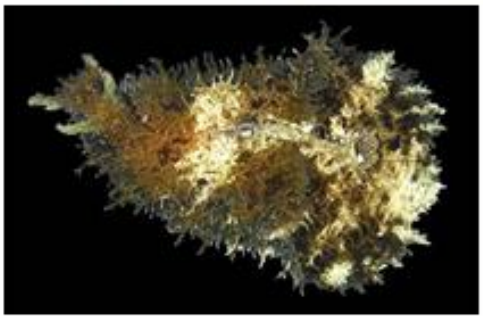
Dolastatin-10

➢ Dolastatin-10: from Indian ocean, in clinical trials, was originally isolated from the sea hare Dolabella.



➢ It inhibits the polymerization of purified tubulin, and inhibits microtubule assembly dependent on microtubule-associated proteins.

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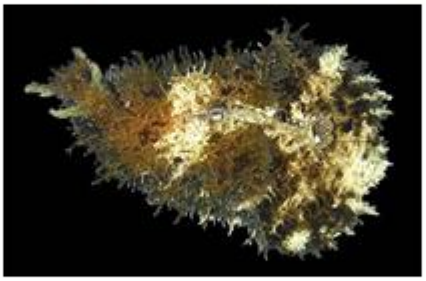

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Ecteinascidin 743

Ecteinascidin-743 (ET-743):

- A tetrahydroisoquinoline alkaloid was isolated from *Ecteinascidia turbinata* a marine invertebrate.
- Ecteinascidin-743 (ET-743) is a natural marine compound, with a unique mechanism of action.

- **[Mechanism of action:**

1. The compound's chemical interactions trigger a cascade of events that interfere with several transcription factors, DNA binding proteins, and DNA repair pathways, likely to be different from other DNA-interacting agents.
2. Trabectedin (ET-743) also causes modulation of the production of cytokines and chemokines by tumor and normal cells, suggesting that the antitumor activity could also be ascribed to changes in the tumor microenvironment.]

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