STEROIDS, CARDIAC GLYCOSIDES & TRITERPENOIDS (Liquorice, Dioscorea and Digitalis)

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Cardiac glycosides

- Cardiac glycosides are a class of organic compounds that increase the output force of the heart and decrease its rate of contractions by acting on the cellular sodium-potassium ATPase pump.

- Their beneficial medical uses are as treatments for congestive heart failure and cardiac arrhythmias; however, their relative toxicity prevents them from being widely used.

- Most commonly found as secondary metabolites in several plants such as foxglove plants, these compounds nevertheless have a diverse range of biochemical effects regarding cardiac cell function.

CARDIO-ACTIVE GLYCOSIDES

- A small group of plant glycosides **act directly on the heart muscle.**
- These include (but are not limited to cardiac glycosides or cardenolides)
- **Cardenolides are steroidal glycosides** → exert a **slowing and strengthening effect on the failing cardiac muscle.**

Generally, the steroid glycosides are invariably employed in the therapeutic domain primarily for two vital reasons;

- To enhance the tone, excitability and above all the contractility of the cardiac muscle.

- To increase the diuretic action, due principally to the enhanced renal circulation (an inherent secondary action).

Note- Lactones ring is very important for therapeutic activity. Removal of lactone ring or even a slight disturbance to the lactone ring means that the activity is lost.

Classification:

1. Cardenolides- They are C23 steroids that have a 17-β side chain and α, β- unsaturated 5-membered lactone ring. Example: Digitalis, Quabain, Strophanthin etc.

2. Bufadienolide- They are C24 homologues of the cardenolides and carry a doubly unsaturated 6-membered lactone ring at the 17-position. The bufadienolides derived their name from the genetic name for the toad, Bufo (the prototype compound bufalin was isolated from the skin of toads). Example: Squill.

STEROIDAL GLYCOSIDES

- Steroid saponins are similar to the sapogenins and related to the cardiac glycosides.

- Chemically it contains sapogenin with cyclopentano-phenanthrene nucleus. They have ability to interact medicinally and beneficially with the cardiac glycosides, sex hormones, Vitamin D and other factors.

- Diosgenin is the important steroid sapogenin. Recently from these saponins steroid hormones like progesterone, cortisone are obtained by partial synthesis.

- These are distributed in Leguminoseae, Solanaceae, Apocynaceae (dicot) and Liliaceae, Dioscoreaceae, Amaryllidaceae (monocot).

- Example: Diosgenin from dioscorea, hecogenin from safed musali.

TRITERPENOID

- Triterpenoid saponins or sapogenins are plant glycosides and are used in detergents or as foaming agents or emulsifiers and have enormous medical implications due to their antifungal, antimicrobial and adaptogenic properties.

- Triterpene saponins are usually β-amyrine derivatives and some are also α-amyrine and lupeol derivatives.

- It has a pentacyclic triterpenoid nucleus which is linked with either sugar or uronic acid.
- Glycyrrhizin, from liquorice root, is an example of a saponin used for anti-inflammatory purposes in place of cortisone.
- Occurrence in polygonaceae, berberidaceae, umbelliferae, rubiaceae family plants.

LIQUORICE, DIOSCOREA AND DIGITALIS

LIQUORICE/GLYCYRRHIZA

Synonym- Radix Glycyrrhizae, Sweet licorice, Mulethi, Licorice or Liquorice root

Biological Source- It consists of dried, peeled or unpeeled, root, rhizome or stolen of *Glycyrrhiza glabra* Linn.

Family- Leguminosae

Distribution- It is cultivated worldwide. Countries producing liquorice include India, Iran, Italy, Afghanistan, China, Russia, Pakistan, Iraq, Azerbaijan, Uzbekistan and Turkey.

Chemical Constituents:

- Triterpenoid saponin: glycyrrhizin is the major active ingredient and is responsible for the sweet taste, being 50 times sweeter than sugar.

- Glycyrrhetinic acid and the aglycone of glycyrrhizin are also present in the root.

- A wide range of flavonoids (1-1.5%), gives yellow colour to the root: flavonones, mainly liquiritin, chalcones and isoflavonoids, sterols and volatile oils are present.

- Flavonoid includes liquiritin, isoliquiritin, liquiritigenin and rhamnoliquirilin and five new flavonoids-glucoliquiritin apioside, prenyllicoflavone A, shinflavone, shinpterocarpin and 1-methoxyphaseolin from root.

- Glucoronic acid, liquiritoside, isoliquiritoside, liquiritin, isoliquiritin.

- Sugars-Glucose, sucrose, mannitol along with resin and starch.

USES:

- Glycyrrhiza has demulcent (agent that form soothing film over mucus membrane & relieving minor pain and inflammation) & expectorant properties.

- It is used as a masking agent for bitter drugs in pharmaceutical formulations such as quinine, aloe, ammonium chloride etc.

- Due to glycyrrhetinic acid, it is used in place of corticosteroids for treatment of inflammation, rheumatoid arthritis and addision's disease.

- Due to flavonoid with anti gastric ulcer effect it is used in peptic ulcer. It also has antispasmodic activity.

- Ammoniated glycyrrhiza is employed as flavouring agent.

- Liquorice is primarily used as a flavouring agent in the tobacco and candy industries and in pharmaceutical and beverage industries.

Note: It should be used in moderation and should not be prescribed for pregnant women or people with high blood pressure, kidney disease or taking digoxin based medication.

Chemical Test: When 80% sulphuric acid is added to a section or powder of drug orange yellow colour is produced due to transformation of flavone glycoside liquiritin to chalcone glycoside isoliquiritin.

DIOSCOREA

Synonym- Yam, Rheumatism root

Biological Source- Dioscorea consists of the dried tubers of Dioscorea species like *Dioscorea deltoidea, Dioscorea compositae* and *Dioscorea floribunda*

Family- Dioscoreaceae

Distribution- Dioscorea is found in North America, Japan, China, Maxico, India and Nepal. In India, the plant grows wildly in Western Himalayas, Karnataka, Kashmir, West Bengal.

Chemical Constituents

- The chief constituents are steroidal saponin glycosides: Dioscin and its aglycone is diosgenin, smilagenin, epismilagenin and β-isomer yammogenin.
- In small portion hecogenin also present.
- Other reported constituents are Resin-Botagenin, Alkaloids (dioscorine), Sterol (Cholesterol, Stigmasterol, P-sitosterol), Enzyme (Sapogenase).

Uses:

1. Diosgenin is used as a precursor for the synthesis of many steroidal drugs like corticosteroids, sex hormones and oral contraceptives.
2. It is also used in rheumatism.
3. Starch also isolated from Dioscorea.

Commercial use- This is widely used in modern medicine in order to manufacture progesterone and other steroid drugs.

How safe is it?

- **Contraindications** Contraindications have not yet been identified.
- **Pregnancy/nursing** Information regarding safety and efficacy in pregnancy and lactation is lacking.
- **Interactions** None well documented.
- **Side Effects** A clinical study evaluating the daily consumption of wild yam reported no adverse events. Topical preparations of wild yam extract are relatively free from adverse effects. Based on a single study in rats, oral *D. villosa*should be avoided in people with compromised renal function.
- **Toxicities** Topical *D. villosa* (with an upper limit of 3.5% diosgenin) was found to not be toxic.

DIGITALIS

Synonym- Foxglove, fairy gloves, purple foxglove or lady's glove, Digitalis leaves

Biological source- Digitalis consists of dried leaves of *Digitalis purpurea* Linn. (The word purpurea has been derived from the purple color of the flower).

Family- Plantagenaceae


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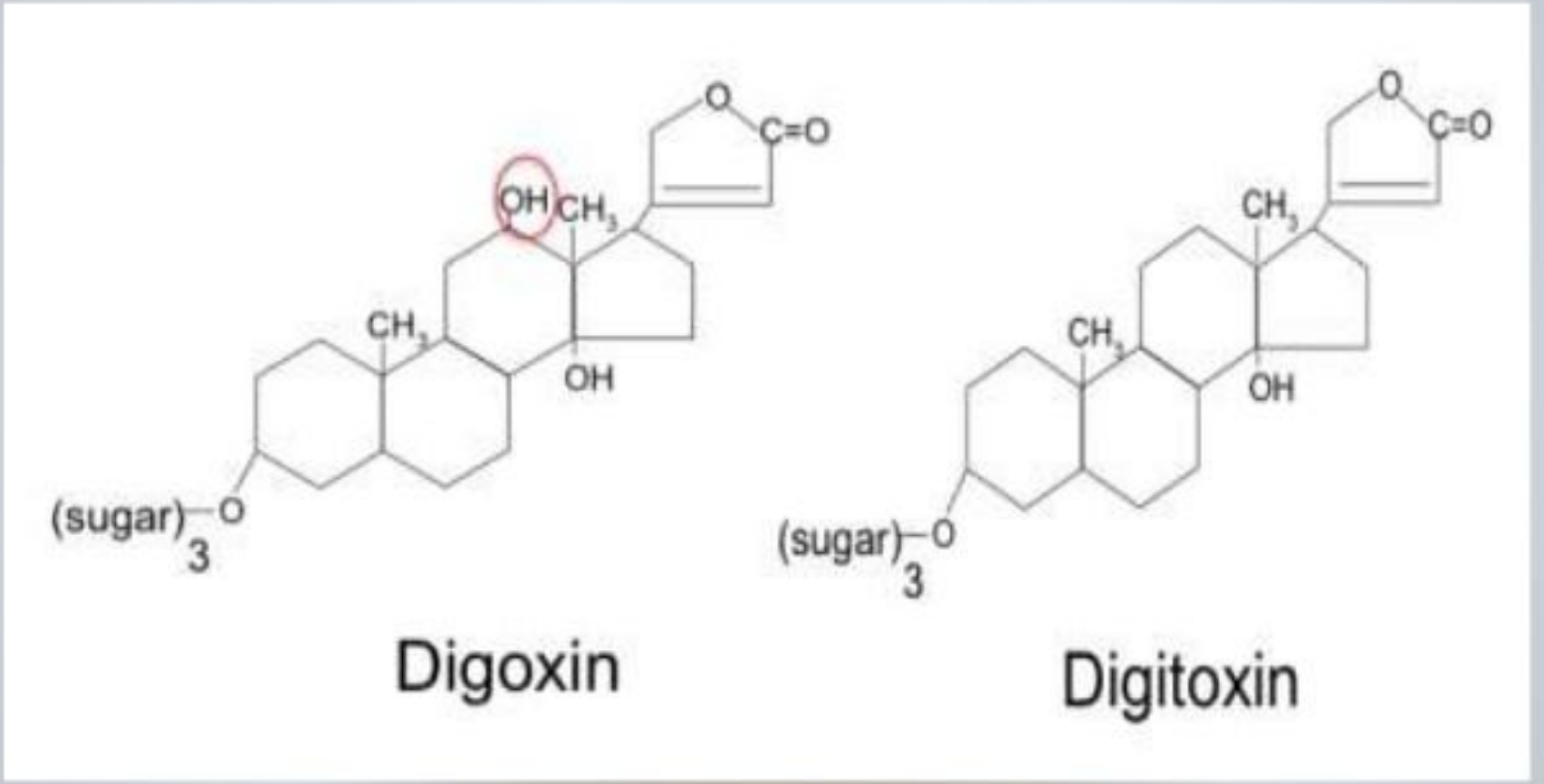
Distribution- This genus is native to western and southwestern Europe, western and central Asia and northwestern Africa. It is found in England, France, Germany, North America and India. In India, it is cultivated in Kashmir and Nilgiri Hill.

Chemical Constituents:

- Digitalis contains three important primary cardiac glycosides- Purpurea glycoside A, Purpurea glycoside B and Purpurea glycoside C which on hydrolysis give rise to digitoxin, gitoxin and gitalin respectively.

- These secondary glycosides on further hydrolysis yields non-carbohydrate moieties i.e. aglycones or genins:digitoxigenin,gitoxigenin and gitaligenin or gitaloxigenin respectively.
- Other reported glycosides are digitalin, diginin, odoroside H, gitaloxin, verodoxin and glucoverodoxin.
- Saponins (digitonin, gitonin and digitosaponin), Tannins, pectins, gallic, formic, acetic, succinic and benzoic acids.

CHEMICAL STRUCTURE OF DIGOXIN AND DIGITOXIN:



Increase contractility Of cardiac cell by increasing free Ca++ concentration

BY

1. Inhibition of Na+/K+ ATPase → increase in intracellular Na+ → increase intracellular Ca++
2. It directly facilitates entry of Ca++ to cardiac cells
3. Increase release of Ca++ from sarcoplasmic reticulum

Uses:

1. Digitalis has cardiotonic activity. It is used in treatment of congestive heart failure.

1. Digitalis along with its various marketed preparations used in the management of atrial flutter, atrial fibrillation, supraventricular tachycardia and premature extra systoles.

1. It enhances the force of contraction of heart muscle which ultimately affords an increased cardiac output, decreased venous pressure and all above decreased blood volume.

Drug	Mechanism/effect	Suggested clinical management
Amiodarone	Decrease in renal and non-renal clearance; can increase SDC by 70%-100%	Monitor SDC and anticipate the need to reduce the dose by 50%
Antacids	Concurrent administration may decrease digoxin bioavailability 25%-35%	Space doses at least 2h apart or avoid concurrent use if possible
Neomycin, sulfasalazine	Decrease in bioavailability by 20%-25%	Space doses at least 2h apart or avoid concurrent use if possible
Erythromycin Tetracyclines	Alter gut bacterial flora; bioav-ailability and SDC increase 40%-100% in about 10% of patients who extensively metabolize	Monitor SDC and anticipate the need to reduce the dose; avoid concurrent use if possible

Drug Interaction

Cholestyramine, colestipol	Bind digoxin in gut and decrease bioavailability 20%-35%; may also decrease enterohepatic recycling	Space doses at least 2h apart or avoid concurrent use if possible
Diuretics	Thiazides or loop diuretics may cause hypokalemia and hypo-magnesemia thereby increasing the risk of digitalis toxicity	Monitor and replace electrolyes if necessary.
Kaolin –pectin	Large doses (30-60ml) may decrease digoxin bioavailability by about 60%	Space drugs at least 2h apart or avoids concurrent use if possible.
Metoclopramide	Increase in gut motility may decrease bioavialability due to decrease digoxin absorption.	Effect is minimized by administration of digoxin capsules
Propantheline	Decrease in gut motility may increase bioavailablilty due to increase digoxin absorption	Effect is minimized by administration of digoxin capsules
Quinidine	Decrease in renal and non-renal clearance; also displacement of digoxin	Monitor SDC and adverse effects; anticipate the need to reduce the dose by 50%

Contraindications

- Compounds that have absorable calcium when used always decrease the dose of cardiotonic glycosides.
- Drugs that cause the deppression of Potassium within the cell, should be used in caution with cardiac glycosides.
- Digoxin is contraindicated with patients having ventricular fibrillation.
- It should be used with caution during pregnancy and breast feeding.

Toxicity

- Abdominal pain
- Fatigue
- Ventricular tachycardia
- Ventricular fibrillation
- Hyperkalemia

THANK YOU