Herbal Medication and Nutraceuticals for the Management of Hypertension, Dyslipidemia and Atherosclerosis

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CARDIAC GLYCOSIDES
Heart diseases can be primarily grouped into three major disorders:

- Cardiac failure, Ischemia and Cardiac arrhythmia.

Cardiac failure can be described as the inability of the heart to pump blood effectively at a rate that meets the needs of the metabolizing tissues.

This occurs when the muscles that perform contraction and force the blood out of heart are performing weakly.

Thus cardiac failures primarily arise from the reduced contractility of heart muscles, especially the ventricles.

Reduced contraction of heart leads to reduced heart output but new blood keeps coming in resulting in the increase in heart blood volume. The heart feels congested. Hence the term congestive heart failure.

Congested heart leads to lowered blood pressure and poor renal blood flow. This results in the development of edema in the lower extremities and the lung (pulmonary edema) as well as renal failure.
• Increasing the force of contraction of the heart (positive inotropic activity) is very important for most heart failure patients. There are several mechanisms by which this could be achieved. Cardiac steroids are perhaps the most useful.

• The cardiac glycosides are an important class of naturally occurring drugs whose actions include both beneficial and toxic effects on the heart.

• Plants containing cardiac steroids have been used as poisons and heart drugs at least since 1500 B.C. Throughout history these plants or their extracts have been variously used as arrow poisons, emetics, diuretics, and heart tonics.

• In large doses they are toxic and bring about cardiac arrest in systole, but in lower doses they are important drugs in the treatment of congestive heart failure.

• They have a diuretic activity. Since, the improved circulation tends to improve renal secretion, which relieves the edema often associated with heart failure.
Distribution in nature

• **Cardiac glycosides** occur in small amounts in the seeds, leaves, stems, roots or barks of plants of wide geographical distribution, particularly of the Family:
  
  ✓ **Apocyanaceae** (e.g. seeds of *Strophanthus*, roots of *Apocynum* and fruits of *Acokanthera*);
  
  ✓ **Scrophulariaceae** (e.g. leaves of *Digitalis sp.*),
  
  ✓ **Liliaceae** (e.g. scales of the bulbs of *Urginea* and *Convallaria*), and
  
  ✓ **Ranunculaceae** (Adonis).

• Cardiac glycosides are also found in **animals**, only in exceptional cases: **Bufadienolides occur in toads** (*Bufo*).
Structure of Cardiac Glycosides

- Cardiac glycosides are composed of two structural features: the sugar (most often an oligosaccharide) and the non-sugar (aglycone-steroid) moieties.
A. Structure of the aglycones

- All of the aglycones have in common the tetracyclic, steroidal nucleus.
- The A, B, C and D rings normally have a *cis-trans-cis* configuration or less often, a *trans-trans-cis* configuration.
- Also common to all the aglycones is the presence of two hydroxyl groups: one is a *3β* secondary alcohol, the other is a *14β* tertiary alcohol.
- All of the aglycones have a β constituent at C-17: an α,β-unsaturated lactone.
- The lactone ring at the 17-position defines the class of cardiac glycoside.
  a) Cardenolides (C23) having an α,β-unsaturated γ-lactone (butyrolactone ring = butenolide)
  b) Bufadienolides (C24) having an di-unsaturated δ-lactone (= pentadienolide)
The name **digitoxin** refers to a agent consisting of **digitoxigenin** (aglycone) and **sugar moieties** (three). **Digoxin** refers to a agent consisting of **digoxigenin** (aglycone) and **sugar moieties** (three). The aglycone portion of cardiac glycosides is more important than the glycone portion.
B. Structure of the sugar moiety

- The sugar moiety is generally linked to the aglycone through the hydroxyl group at C-3.

- The majority of the saccharides found in cardiac glycosides are highly specific:
  1. 2,6-dideoxyhexoses, e.g. D-digitoxose
  2. 2,6-dideoxy-3-methylhexoses, e.g. D-diginose
  3. 6-deoxyhexoses, e.g. L-rhamnose
  4. 6-deoxy-3-methylhexoses, e.g. D-digitalose
  5. Hexose, e.g. glucose (when there is a glucose unit, it is always terminal).

- The sugars can modify the activity (potency, toxicity), the solubility, the diffusion through membranes, the rate of absorption and transportation of the glycosides.
Cardenolides

• Their structure is closely related to bufadienolides but these C23 steroids possess a butenolide ring located at C-17. The structure of digitoxigenin is given below as a typical example of cardenolides.

• They are widely distributed in plants mainly as glycosides and are either toxic or insect deterrents.

• These steroids were largely studied as potent cardiotonics.

• Monarch butterfly is well known to be highly toxic to birds because of cardenolides which come from the milkweed leaves eaten by its caterpillar.
• Cardenolides (most prevalent) are **C23 steroids**.

• Cardenolides have a hormonal nature as substances. Their effects are on the **heart** and **kidney**.

• Strong, bitter and disagreeable taste.

• **Cardiotonic** = affect contractions of the heart muscle.

• Break down in fermentation by enzymatic action.

• Symptoms of poisoning include dizziness, vomiting, irregular heart beat, and delerium or hallucinations.

• Treatment: atropine and activated charcoal, lidocaine

**Assumed mechanism of action:**

• **Inhibition of the Na+, K+-ATPase** resulting in increased intracellular sodium and subsequent intracellular calcium leading to **enhanced muscle contraction in cardiac tissue**.
Bufadienolides

- They are typically polyhydroxy C24 steroids with a pentadienolide ring at C-17. The structure of hellebrigenin is given below as a typical example of bufadienolides.

![Hellebrigenin structure](image)

- They have been isolated from plants and animals. More than 250 compounds have been identified.

- In plants, they are mostly glycosides with one to three sugars in a chain linked to the 3-hydroxyl group. They are important for their cardiotonic activity.

- Furthermore, they possess insecticidal and antimicrobial properties, those produced by the toad skin are strongly poisonous.
Structure - Activity Relationships

- The sugar moiety possesses no biological activity, but its presence enhances the activity and modulates it by modifying the polarity of the compound.

- The **cardiac activity is linked to the aglycone**.

- **A/B cis fusion is important** (not mandatory). Conversion to A/B trans system leads to a marked drop in activity.

- **C/D cis fusion is important.** Structures with C/D trans fusion are inactive.

- The **lactone at C-17**, must be in the **β-configuration**.

- The **unsaturated 17-lactone plays an important role in receptor binding**. Saturation of the lactone ring dramatically reduced the biological activity.

- The lactone ring is not absolutely required. For example, using a,b-unsaturated nitrile (C=C-CN group) the lactone could be replaced with little or no loss in biological activity.
Digitalis glycosides

Several species of *Digitalis* yield pharmacologically active principles. The most important of these species are *Digitalis purpurea* and *Digitalis lanata*.

1. *Digitalis purpurea* (Purple foxglove leaves)
   0.15% – 0.4% total cardenolides, ~ 30 glycosides
   Purpurea glycosides A and B (~60%),
   *digitoxin* (~12%), *gitoxin* (~10%) and
   gitaloxin (~10%).

2. *Digitalis lanata* (White foxglove leaves)
   0.5% – 1.5% total cardenolides, ~ 60 glycosides
   Lanatosides A and C (~50%),
   lanatosides B, D, E as well as *digoxin* and *digitoxin*. 
**Digitalis purpurea** (Purple Foxglove)

- **Biological Source:** Dried leaves of *Digitalis purpurea*.
- **Family:** Scrophulariaceae
- **Parts Used:** Leaves
- **Habitat:** Native to Western Europe. Although the plant is cultivated, wild plants are thought to be superior.
- Also contains Anthraquinone glycosides, Saponins, Sopogenins, Flavonoids

**Medical Uses:**
- Tonic effect on the diseased heart.
- Glycosides enable the heart to beat more strongly, slowly and regularly, without using or needing more O₂.
- Stimulates urine production - lessening the load on the heart.
Some cardioactive glycosides from *D. lanata*:

<table>
<thead>
<tr>
<th>Glycoside</th>
<th>Aglycone</th>
<th>Sugar moieties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanatoside A</td>
<td>Digitoxigenin</td>
<td>Glucose–acetyldigioxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Acetyldigoxin</td>
<td>Digitoxigenin</td>
<td>Acetyldigoxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Digitoxigenin</td>
<td>(Digitoxose)$_3$–</td>
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<tr>
<td>Glucoevatromonoside</td>
<td>Digitoxigenin</td>
<td>Glucose–digitoxose–</td>
</tr>
<tr>
<td>Digitoxigenin-O-glucosyl-6-deoxyglucoside</td>
<td>Digitoxigenin</td>
<td>Glucose–glucosylmethylse–</td>
</tr>
<tr>
<td>Glucodigifucoside</td>
<td>Digitoxigenin</td>
<td>Glucose–fucose–</td>
</tr>
<tr>
<td>Lanatoside B</td>
<td>Gitoxigenin</td>
<td>Glucose–acetyldigioxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Glucogitoroside</td>
<td>Gitoxigenin</td>
<td>Glucose–digitoxose–</td>
</tr>
<tr>
<td>Digitalinum verum</td>
<td>Gitoxigenin</td>
<td>Glucose–digitoxose–</td>
</tr>
<tr>
<td>Lanatoside C</td>
<td>Digoxigenin</td>
<td>Glucose–acetyldigioxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Acetyldigoxin</td>
<td>Digoxigenin</td>
<td>Acetyldigoxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Deacetyl-lanatoside C</td>
<td>Digoxigenin</td>
<td>Glucose–(digitoxose)$_3$–</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxigenin</td>
<td>(Digitoxose)$_3$–</td>
</tr>
<tr>
<td>Digoxigenin-glucosyl-bis-digitoxosite</td>
<td>Digoxigenin</td>
<td>Glucose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Lanatoside D</td>
<td>Digoxigenin</td>
<td>Glucose–acetyldigioxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Lanatoside E</td>
<td>Gitaloxigenin</td>
<td>Glucose–acetyldigioxose–(digitoxose)$_2$–</td>
</tr>
<tr>
<td>Glucolanadoxin</td>
<td>Gitaloxigenin</td>
<td>Glucose–digitoxose–</td>
</tr>
<tr>
<td>Glucoverodoxin</td>
<td>Gitaloxigenin</td>
<td>Glucose–digitoxose–</td>
</tr>
</tbody>
</table>

Ref: Trease & Evans
Digitoxin Vs Digoxin

- **Digitoxin** is a cardiotonic glycoside obtained from *D. purpurea, D. lanata*.
- It is the most lipid-soluble of the cardiac glycosides used in therapeutics.
- The major pharmacokinetic parameters for digitoxin include complete oral absorption, which distinguishes it from other cardiac glycosides.
- Digitoxin may be indicated in patients with impaired renal function.

- **Digoxin** is the most widely used of the cardiotonic glycosides, and it is obtained from the leaves of *D. lanata*.
- It is a highly potent drug and should be handled with exceptional care.
- Digoxin tablets are 60 to 80% absorbed.
- Digoxin is indicated when the risk of digitalis intoxication is great, since it is relatively short-acting and rapidly eliminated when compared with digitoxin.
**Strophanthus glycosides**

**Botanical Name:** *Strophanthus kombe*

**Family:** Apocynaceae

**Part Used:** **Dried seeds** (ripe)

The principle glycosides are:

1. K-strophanthoside
2. K-strophanthin-β
3. Cymarin

**Habitat:** East Africa. It is not a cultivated species and is usually seen growing as a wild plant. It is not typically seen growing in other regions.
Uses

- **Uses** - similar to *Digitalis*
- Chronic cardiac weakness
- Diuretic action (thought to be more powerful than *Digitalis*)
- Can be administered IV
- **Actions**
  - Similar to *Digitalis*
  - **POISONOUS**
Squill glycosides

0.1% – 2.4% total bufadienolides, ~15 glycosides

- **White variety:**
- **Botanical Name:** *Urginea maritima*
- **Family:** Liliaceae
- **average 0.2%-0.4%** proscillaridin A, scillaren A, glucoscillaren A, scilliphaeoside, scilliglaucoside *(aglycone: scillarenin)*

- **Red variety:** < 0.1% scilliroside and glucoscilliroside *(aglycone: scillirosidin)*;
  proscillaridin A and scillaren A as in the white variety

- **Habitat:** This squill is native to coastal regions of the Mediterranean in sandy soil, but it is widely cultivated.

Pharmacological properties of squill

- **White squill:** It is an expectorant, but it also possesses emetic, **cardiotonic** (proscillaridin A), and **diuretic** properties.

- **Red squill:** It is used as a **rat poison (scilliroside)**, because rodents lack the vomiting reflex, which makes red squill particularly lethal to these animals.
Scillae bulbus

Scillarenin: $R_1 = \text{CH}_3$, $R_2 = \text{H (Aglycon)}$
Proscillaridin A: $R_1 = \text{CH}_3$, $R_2 = \text{Rham}$
Scilliphaeoside: $R_1 = \text{H}$, $R_2 = \text{Rham}$
Scillaren A: $R_1 = \text{CH}_3$, $R_2 = \text{Gluc-Rham}$
Glucoscillaren A: $R_1 = \text{CH}_3$, $R_2 = \text{Gluc-Gluc-Rham}$
(3β,6β)-6-(Acetyloxy)-3-(β-D-glucopyranosyloxy)-8,14-dihydroxybufa-4,20,22-trienolide
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 seeds are used part of the plant, *Aesculus hippocastanum* (family *Hippocastanaceae*), native to western Asia and Balkan and now widely distributed all over the world as ornamental plant.

The seeds have long been used for their saponin content like aescin.

It also contains flavonoids like quercetin, kaempferol, and coumarins and tannins.

- **USES:** The plant is traditionally used for peripheral vascular disorders including haemorrhoids, deep vein thrombosis, varicose veins, prevents edema.
- It is also used as anti-inflammatory due to its content of flavonoides, coumarins.
- Coumarins cause a thinning of the blood, so should not be taken with anticoagulants.
RUTIN
(Flavonoid Glycoside)

• Chemically rutin is $5, 7, 3', 4'$-tetrahydroxy flavonol 3-rhamnoglucoside.

• On hydrolysis, it gives quercetin and the two sugar varieties which are called Rutinose. It is prepared from rutin by hydrolysis with the enzyme rhamnodiastase.

• Rutin is usually isolated from *Fagopyrum esculentum* and Family Polygonaceae

• Rutin was first isolated from the leaves of *Ruta graveolens* (Rutaceae)

*Fagopyrum esculentum*  
*Ruta graveolens*
Uses

1. Rutin has been used to decrease capillary fragility and permeability in cases of hypertension and radiation injuries.

2. Anti-inflammatory properties that may be beneficial for various types of dermatitis, an itchy skin inflammation.

3. According to the University of Maryland Medical Center, taking 50 to 250 mg of a rutin supplement two or three times a day may help relieve symptoms of allergic contact skin reactions, as well as eczema and seborrheic dermatitis التهاب الجلد الدهني which causes dandruff.

4. Rutin also may be helpful for treating various types of erythema, a condition involving skin redness or rash caused by health conditions.
**Malvidin: Blue Berry, Bilberry, European Berry (Vaccinium myrtillus)**

- Blue berry is rich in **phenolic acids**, **flavonoids** (hyperin, quercitin) and **anthocynin 0.5 %** such as cyanidin, delphinidin and malvidin.

![Malvidin molecule](image)
Pharmacological activity:

Blue berry anthocyanins have:

1. Vascular protection.
2. Anti-edemic effect.
3. It lowers cholesterol and total lipid levels.
4. The plant also has anti-atherosclerotic effect with anti-platelet effect.
5. Anti-inflammatory effect.
6. Clinically, it is used for eye disease such as retina bleeding risk.
7. It has a free radical-scavenging activity (Anti-oxidant).
8. It alleviates the cognitive decline occurring in Alzheimer disease and other conditions of aging.
9. It prevents urinary tract infection.
Garlic

- It consists of the bulb of *Allium sativum* and Family: Liliaceae.
- The intact cells of garlic contain an odorless, sulfur-containing amino acid derivative (++)-S-allyl-L-cysteine sulfoxide, commonly known as alliin.
- **Aliin** is hydrolyzed by the effect of alliinase enzyme present in different cells after crushing into **allicin** (diallyl thiosulfinate).
- **Allicin** is responsible for the characteristic odor and flavor of garlic.
- **Allicin** is a potent antibacterial, anti-hyperlipidemic, and it inhibits platelet aggregation and enhances the blood fibrinolytic activity.
- Garlic preparations found to effectively lower total cholesterol and LDL cholesterol in adults with high cholesterol if taken for longer than two months. It also moderately raised HDL cholesterol.
Garlic

Dose:

• Encapsulated Powder: 600 to 900 mg/day (standardized to yield 6 mg allicin)
• Aged garlic capsules: similar dose to above
• Fresh bulb: 1 clove/day prophylactically

Safety:

• Safe for long-term use; side effects may include occasional GI disturbances.
• Case reports suggest garlic is associated with increased bleeding tendency, so use caution before and after surgery (10 days before, 3 days after) and w/anticoagulants and antithrombotic agents.
• Caution with warfarin and HIV protease inhibitors (i.e. saquinavir); high doses (>5g fresh garlic/day) contraindicated with warfarin.
Hawthorn

- Hawthorn is a plant.
- **Botanical name:** *Crataegus monogyna*, *C. oxyacantha*, *C. laevigata*
- The **leaves, berries, and flowers** of hawthorn are used to make medicine.
- Hawthorn is used for diseases of the **heart** and **blood vessels** such as congestive heart failure (CHF), chest pain, and irregular heartbeat.
- It is also used to treat both **low blood pressure** and **high blood pressure**, “hardening of the arteries” (atherosclerosis), and **high cholesterol**.
Hawthorn

How does it work?

• It improves the amount of blood pumped out of the heart during contractions, widen the blood vessels, and increase the transmission of nerve signals.

• Hawthorn contains proanthocyanidin which has blood pressure-lowering activity and cause relaxing of the blood vessels farther from the heart.

• Hawthorn can lower cholesterol, low density lipoprotein (LDL, or “bad cholesterol”), and triglycerides (fats in the blood). It seems to lower accumulation of fats in the liver and the aorta (the largest artery in the body, located near the heart). It also seems to have antioxidant activity.

Other uses:

• Some people use hawthorn for digestive system complaints such as indigestion, diarrhea, and stomach pain.

• Hawthorn is also used to treat tapeworm and other intestinal infections.

• It is also used to reduce anxiety as a sedative, to increase urine output, and for menstrual problems.

• Some people apply hawthorn to the skin for boils, sores, and ulcers.

• It is also used as the ingredients in candied fruit slices, jam, jelly, and wine.
Thank You