Faculty of Pharmacy

Anthraquinones

Pharmacognosy and Phytochemistry

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Anthraquinone Glycosides

- The anthraquinone moieties are 5 general groups and these are derived from:

- Anthraquinone
- Anthranol
- Anthracene
- Anthrone
- Anthranol

Anthraquinone Derivatives

- Anthracene
- Oxaanthrone
- Diamaanthrone
- Anthrone
- Anthranol
The free anthraquinone aglycones exhibit little therapeutic activity.

The sugar residue facilitates absorption and translocation of the aglycone to the site of action.

The anthraquinone and related glycosides are stimulant cathartic and exert their action by increasing the tone of the smooth muscle in the wall of large intestine.

A research on rhein glycosides shows that this compound increases pressure on the walls of the colon \{They are irritant and stimulate peristaltic movement\}, thus pushing the stools outside.

We have 4 general types of anthraquinone glycosides according to the differences in the chemical structure, and these are:
1. **Emodin:**

![Emodin structure](image)

1, 3,8-trihydroxy-6-methyl anthraquinone

2. **Aloe-emodin:**

![Aloe-emodin structure](image)

1,8-dihydroxy-3-(hydroxymethyl)-9,10-anthraquinone

1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione.

3. **Rhein:**

![Rhein structure](image)

4, 5-dihydroxy -9,10-dioxoanthracene-2-carboxylic acid

4. **Chrysophanol:**

![Chrysophanol structure](image)

1, 8-dihydroxy -3-methyl anthraquinone
**Biosynthesis:**

- The biosynthesis of all secondary metabolites have revealed the existence of 3 very important biosynthetic routes: the acetate, mevalonate and shikimic acid pathway.

- Most anthraquinone glycosides aglycones are derived from the acetate pathway, which usually starts from acetic acid units which will form the active form *acetyl Co enzyme A*, which will then form the *malonyl Co enzyme A* by the addition of another acetate unit.

\[
\text{Octaketide synthase} + \text{Acetyl coenzyme A} + \text{Malonyl coenzyme A} \rightarrow \text{Anthraquinone}
\]

**Biosynthesis of Anthraquinones**

- Mainly produced via acylpolymalonate (acetate-malonate) pathway in Polygonaceae & Rhamnaceae & Leguminosae....

- Starts with *acetyl CoA* carboxylation to *malonyl CoA* then continues in the usual way of formation of the poly-keto-methylene-chain with simultaneous loss of CO₂ followed by cyclisation.

- Shikimate-mediated in Rutaceae, Rubiaceae & Gesneriaceae
In the biosynthesis of the **anthraquinones** for the formation of the poly-keto-methylene-chain: **1 acetyl CoA and 7 Malonyl CoA** are used.

\[
\text{CH}_2\text{C-S-ACP} + 7\text{Malonyl-ACP} \rightarrow \text{Beta-Polyketo acid}
\]

\[
\text{Frangulinolin} \quad \text{Frangulomedin salicin}
\]

**DRUGS CONTAINING ANTHRAQUINONES:**

1. *Cascara sagrada: القشرة المقدسة*
   - Is the dried bark of *Cascara purshiana* [Rhamnaceae
   - النبّاق، النبّاقات، السدريات, السدريات].

Native to western North America

The Bark
It should be aged for at least one year prior to use in medicinal preparations as a cathartic.

Reduced forms of emodin-type glycosides predominate in fresh bark which is oxidized to the anthraquinones after this one year of aging.

Reduced forms \(\rightarrow\) anthraquinones \\
(Anthrone and anthranol) \(\rightarrow\) (less active)

Constituents:
- Two types of anthracene compounds (6-9%) and these consist of:
  - a) C-glycosides 80-90%
  - b) O-glycosides 10-20%.
  - c) mixture of both.

O-glycosides: the principle O-glycosides are of aloe-emodin type which are cascarosides A, B, C, D.

Cascaroside A, B, C, and D
All Include:
- O-glycosides.
- C-glycosides.
Uses, indication and action: laxative (adj.) = purgative (adj.) = a cathartic (noun).

2. Rhubarb: الرواند
The main constituent is **rhein** which is **rhein-8-glucoside**.

![Rhein-8-Glycoside](image)

**Uses, indications and action:** laxative (adj.) = purgative (adj.) = a cathartic (noun).

3. **Aloe**

- **Dried juice** obtained by evaporation of the liquid drained from the transversely cut leaves of various species of aloe.
  
  a) **Aloe barbadensis (vera)**: (F. Liliaceae): which will form **Curacao aloe** (common name).
  
  b) **Aloe ferox**: **Cape aloe** (common name).
  
  c) **Aloe perryi**: **Zanzibar variety** (common name).

Also, contains **TANNINS**

That are constipative, therefore rhubarb is a **MILD LAXATIVE**
- **Constituents:**
  
  a) The main constituent is **barbaloin** which is a C-glycoside.  
  - It is a mixture of **aloin A** (10-R-isomer) and **aloin B** (10-S-isomer).

  ![Aloin A structure](image1)

  - **Aloin A differs from aloin B just by the orientation of the substituents on C-10.**

  ![Aloin B structure](image2)

  ![Aloin A structure](image3)

  - **O-glycoside** of barbaloin called **aloinoside A & B**, where instead of the H-atom at number 3, there is an α-rhamnose moiety.

  ![Aloinoside A & B](image4)

  - **Aloinoside A differs from aloinoside B just by the orientation at C-10.**
• **Uses:**
  1. **Laxative.**
  2. The juice which is a complex structure contains polysacharrides used for *wound healing* and *burns*, (for skin as gel).

4. **Senna:**
   - Dried leaflets of:
     - *Cassia acutifolia*: (Alexandrian senna)
     - *Cassia angustifolia*: (Indian senna or Tinnevelly senna)
   - Both belong to the family **Leguminosae** or **Fabaceae**.

*Alexandrian senna*
• **Constituents:**
  - The main constituents are **O-glycosides sennosides** which are an example of dianthrones and these are dimeric glycosides.
  - The aglycones are **aloe-emodin** and **rhein** type and these are:
    - R2
    - Sennoside A: COOH trans
    - Sennoside B: COOH cis
    - Sennoside C: CH₂OH trans
    - Sennoside D: CH₂OH cis

This implies that sennoside A and B, which are the main components, are **dianthrones** and have their aglycones as **rhein** but **sterioisomers** (i.e. trans and cis at the connection bridge 10-10').

Sennoside C and D are **heterodianthrones**, i.e. the aglycones are **rhein** and **aloe-emodin**.

**Uses and action:** laxative and cathartic at dose of **2g**.
Anthraquinone laxatives should not be the first choice for treatment of constipation. Bulk laxatives are preferable.

Bulk laxatives: increase the bulk in stool, an effect that helps cause movement of the intestines. It also works by increasing the amount of water in the stool, making the stool softer and easier to pass.

The smallest dose that gives a satisfactory effect should be chosen.

CONTRAINDICATIONS:
1. Intestinal occlusion.
2. Acutely inflammatory intestinal disease.
3. Appendicitis.
### Laxatives

<table>
<thead>
<tr>
<th>Laxative Type</th>
<th>Generic Name</th>
<th>Brand Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming</td>
<td>Methylcellulose</td>
<td>Citrucel®</td>
</tr>
<tr>
<td></td>
<td>Polycarbophil</td>
<td>FiberCon® Fiber lax®</td>
</tr>
<tr>
<td></td>
<td>Pyrillium</td>
<td>Netamsuc® Koraryl®</td>
</tr>
<tr>
<td>Lubricating</td>
<td>Glycine</td>
<td>Glycine suppository (generic)</td>
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<tr>
<td></td>
<td>Mineral oil</td>
<td>Mineral oil (generic)</td>
</tr>
<tr>
<td></td>
<td>Magnesium hydroxide (milk of magnesia) and mineral oil</td>
<td>Philips® Magn-O</td>
</tr>
<tr>
<td>Stool Softeners</td>
<td>Docusate sodium</td>
<td>Colace®, Dulcolax® Stool Softener, Phillips® Liqui-Gel®</td>
</tr>
<tr>
<td>Saline</td>
<td>Magnesium hydroxide (milk of magnesia)</td>
<td>Ex-Lax® Milk of Magnesia Laxatite/Astacid Phillips® Chewable Tablets Phillips® Milk of Magnesia</td>
</tr>
<tr>
<td>Stimulant</td>
<td>Bisacodyl</td>
<td>Ex-Lax Ultra™ Dulcolax Bowel Prep Kit</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate and osalassium bitartrate</td>
<td>Geo Two Emuquant®</td>
</tr>
<tr>
<td></td>
<td>Sennosides</td>
<td>Ex-Lax® Laxative Pills</td>
</tr>
<tr>
<td></td>
<td>Castor oil</td>
<td>Purge®</td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>Senokot®</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Polyethylene glycol 3350</td>
<td>Glycolax®, MiraLAX®</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>Kizelease®</td>
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### Laxative Selections Guidelines

- The initial choice is usually a bulk-forming laxative
- Acute constipation is the primary indication for OTC laxatives. They are also used for preparing for diagnostic GI procedures
- Laxative use is supervised by a physician in patients in whom straining should be avoided (after surgery or MI) or in chronic constipation
- Laxative use is inappropriate in case of intestinal pathology
Side effects of anthraquinone cathartics:

1. **Gastrointestinal compliance.** 10 gm can lead to loss of electrolytes, especially K⁺ (Hypokalemia) which may cause inhibition of intestinal motility.

2. Long term uses can cause albuminuria and hematuria.

3. In rare cases, anthraquinones cause heart arrhythmia, nephropathy, edemas, accelerated bone deterioration.

Interaction:

- Loss of K⁺ ion on long term CAN ENHANCE THE EFFECT OF CARDIAC GLYCOSIDES, increasing their toxicity.
- Anthraquinone glycosides should not be given to pregnant women and children.
Pharmacognosy and phytochemistry - Anthraquinones

Carmine

- A red pigment obtained from the cochineal louse, *Dactylopius coccus* which lives on cactae (singular: cactus) of the genera *Opuntia* and *Napalea* (*Cactaceae*) in Mexico and Peru.

- It has been brought to the West indies, the Canary Island and Spain.

- The dried female insect – the crude drug *cochineal* – contains about 10% of the intensely, red water-soluble colouring matter, *carminic acid*, a C-glycoside of an AQ derivative.

**Carmine**

- **Carmine**: is a concentrate containing about 50% carminic acid {E-120}.
- **Uses**: cochineal and carmine have been used as colouring matter for *lipstick*, *food*, *confectionaries* and *bevergaes*. They are believed to be less harmful than the synthetic pigments.

- Can cause severe allergies and anaphylactic shock.

[Chemical structure of carminic acid]
Hypericin:

- Is a red-coloured, dimeric AQ derivative which is present in the leaves and flowers of Hypericum perforatum (St. John wort).

Biosynthesis:

- Hypericin is formed from two molecules of emodin anthrone by oxidative phenolic coupling (see figure).
Oxidative phenolic coupling is a widespread phenomenon both in the plant and animal kingdoms.

Several enzymes catalyze this reaction. They have an iron or copper as a prosthetic group. (The prosthetic group may be organic (such as a vitamin, sugar, or lipid) or inorganic (such as a metal ion), but is not composed of amino acids. Prosthetic groups are bound tightly to proteins and may even be attached through a covalent bond, as opposed to coenzymes, which are loosely bound).

All are able to affect one-electron transfer.

Hydrogen peroxide and molecular oxygen ($\text{H}_2\text{O}_2$ and $\text{O}_2$), used as oxidants, are ultimately reduced to water.

The transition metal catalysts shift between their oxidized and reduced forms.

For the phenol part, the enzyme removes one electron and the phenoxy radical formed can couple in a number of ways.
Hypericin is a photosensitizing agent and causes the so-called "light sickness" in animals feeding on Hypericum. Animals with white or light-colored coats display the symptoms upon exposure to light following feeding.

Symptoms:
1. Psychomotor excitement (a series of unintentional and purposeless motions that stem from mental tension and anxiety).
2. Efflorescence (redness of skin) in form of blisters like those caused by burns.
3. In serious cases, the poisoning results in:
   a. Hemolysis.
   b. Epileptic fits, and
   c. Death of animals.
Hypericin has **antiviral activity** against *retoviruses* such as *influenza* virus and *Herpes simplex* virus both *in vitro* and *in vivo* presumably **by acting directly on the virus particularly on the membrane components**.

It has no activity on the transcription, translation or transport of viral proteins to the cell membrane and it has also no direct effect on the polymerase (an enzyme that synthesizes long chains or polymers of nucleic acids).

Hypericin has been thought to be responsible for the **antidepressant activity** of extracts of Hypericum.

**Hypericum:**

- Is the dried flowers and aerial parts of St. John Wort, *Hypericum perforatum* (Clusiaceae).
- Is a herbaceous perennial plant which is widely distributed in Europe, Asia and Northern Africa, and now also naturalized in the USA.
Hypericin is the main component among the group of dimeric AQ derivatives present in the plant. Other components are: protohypericin, pseudohypericin and cyclopseudohypericin.

- Differs from hypericin by having a –OH group.

1. Hypericum is a well-known herbal remedy as an anti-inflammatory and wound-healing agent.
2. Also, the ethanol-water extracts of the crude drug are known for their antidepressant activities (daily doses: 200-900 mg).

**The antidepressant activity:**
- The extract inhibits the synaptosomal uptake of norepinephrine, serotonin and dopamine.
- **Induces β-receptor down-regulation and up-regulation** of serotonin 5-HT2 receptors when given subchronically to rats, and is active in a large variety of behavioural models indicative of antidepressant activity.
- However, MAO-A and MAO-B inhibiting properties of the extract are probably too weak to contribute significantly to its antidepressant activity i.e. **Antidepressant activity is probably not due to these inhibitory properties.**

**Note:**
- Serotonin, melatonin, noradrenaline, and adrenaline are mainly broken down by MAO-A.
- Phenethylamine and benzylamine are mainly broken down by MAO-B.
Hypericin might be involved in the antidepressant activity. Most commercial extracts today are standardized on the content of hypericin.

**Interactions of Hypericum:**

- It can interact with many prescribed medicines such as warfarin, cyclosporin, theophylline, digoxin, HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, anticonvulsants (antiepileptics), selective serotonin reuptake inhibitors and oral contraceptives.

- The reason of this interaction is that hypericum (particularly, hyperforin) activates pregnane X receptor (PXR), the receptor that regulates expression of cytochrome P450-3A4 (CYP3A4) monoxygenase. Activation of PXR induces expression of CYP3A4 which is involved in the oxidative metabolism of more than 50% of all drugs, which means more rapid metabolism and hence lower plasma levels of the prescribed medications.
Accordingly, dose adjustment is necessary especially with drugs such as **warfarin** and **cyclosporin** (immunosuppressant drug widely used in organ transplantation to prevent rejection).

In addition, stopping of Hypericum intake while taking such drugs can result in serious problems due to the elevated plasma levels of these medications.

It is noteworthy that hypericin **does not** have any effect on any enzyme member in the cytochrome p-450 family.