

ANTHRAQUINONE (ANTHRACENE) GLYCOSIDES

- Anthraquinone derivatives are the active components in a number of crude drugs with purgative (cathartic) properties.
- Distributed in various families
- Their aglycone is anthracene type
- Many of them are used technically as dyes since anthraquinones are coloured substances.
- Cathartic drugs---Rhizoma Rhei, Aloe, Folia Sennae
- Drugs used as dyes----Coccionella, Radix Rubiae

ANTHRAQUINONES

- They are found in plants as
 1. Oxanthrone
 2. Anthrone
 3. Anthraquinone forms and dimers of these structures
- ANTHRAQUINONE is the most stable form.

ANTHRAQUINONES

- 1,8-dihydroxyanthraquinone derivatives are the ones exhibit purgative activity and important in pharmacy
- Dimerization → Dianthrone/ dianthranol from C10 position with C-C bond.
- O-Glycoside → Glycosylation with -OH in 1, 6, 8, 9, 10. C (e.g.)
- C-Glycoside → Glycosylation from 10. C position, C-C bond

Emodin-L-rhamnoside
Franguloside

Aloin

ANTHRAQUINONES

- R1 (C3) R2 (C6)
- -CH₂OH -H (ALOE-EMODIN)
- -CH₃ -H (CRYSOPHANOL)
- -CH₃ -OH (EMODIN)
- -CH₃ -OCH₃ (PHYSCION)
- -COOH -H (REIN)

ANTHRAQUINONES

- The two anthrone moieties are same

HOMODIANTHRON

rein + rein

ANTHRAQUINONES

EMODIN

➤ The two anthrone moieties are different

HETERODIANTHRON

rein + emodol

ANTHRAQUINONES

- Free anthracene derivatives → %0.2-0.8
- Anthracene glycosides and polymers → %1-7
- In dried drugs, anthranol and anthrahydroquinone amounts will decrease and anthraquinone amount will increase → oxidation

ANTHRAQUINONES

IDENTIFICATION

1) Free anthracens identified with BORNTRAGER reaction;

- Organic solvent extract + alkaline $-OH \rightarrow$ red colour
- Only anthraquinones; glycosides after hydrolised, anthrons and anthronols after oxidisation gives Borntrager reaction

ANTHRAQUINONES

- 2) Anthranols are identified with SCHÖNTETEN reaction
- Water extract + Na-borate → green fluorescent
- 3) Anthrones give different colors with p-nitroso dimethylaniline while anthraquinones doesn't give any color.

ANTHRAQUINONES

QUANTIFICATION

- Quantity in plants depends on;
 - Collection time
 - Method of drying
 - Storage perion
 - Shelf time of drug

ANTHRAQUINONES

1) **COLORIMETRIC ASSAY:** Free anthraquinone quantification with Borntrager reaction (a)

- Reduced derivative: Oxidation with H_2O_2 then apply Borntrager reaction (b)
- **(b-a) → result**

2) **GRAVIMETRIC ASSAY**

3) **BIOLOGICAL ASSAY → Fühner Method**

ANTHRAQUINONES

➤ USAGE-EFFECTS

- 1) Purgative: Increase in large bowel
- Free anthraquinones are less soluble in water; less effective
- Glycosides are polar molecules; they are soluble in water. They are neither resorbed nor hydrolised in small intestines. Hydrolised by beta-glycosidase found in flora of large bowel → released anthraquinones reduced to anthronss which are bioactive. These anthrons increase the peristaltism of bowel and inhibit Na-K ATPase; thus this results with water, natrium and chlorid stay in bowels and this softens the feces.

ANTHRAQUINONES

- Effective in 10-15th hours of intake
- Effective also parenterally
- More phenolic -OH → more efficiency
- Thus; most effective anthraquinone → EMODINE
- Non-effective-----REIN
- Most effective derivatives dianthrone, o-glycosides of anthraquinones and C-glycosides of anthrones, respectively.

ANTHRAQUINONES

Structure-Activity Relationship

1. Situation of phenolic substituents is related with the activity:
 - Hydroxylation at C-1 and C-8 is essential for activity
 - Phenolic substituent in α -position \rightarrow increase in PURGATIVE activity
 - Acetylation of phenolic group \rightarrow decrease in efficiency
2. If drug contains both tannins and anthraquinones \rightarrow decrease in LAXATIVE activity
 - In lower dosage ----- ASTRINGENT
 - In high dosage ---- LAKSATIVES, PURGATIVE

ANTHRAQUINONES

3. Some skin illnesses (psoriasis, dry egzema) → ANTISEPTIC (e.g. Chrysarobin)
4. Veterinary → ANTISEPTIC (e.g. Aloe)

RHIZOMA RHEI (TK), Rhubarb

➤ *Rheum* sp. (Polygonaceae)

➤ 2 sections:

➤ PALMATA SECTION:

➤ *Rheum palmatum*

➤ *Rheum officinale*

- *Rheum palmatum*
- *Rheum officinale*

RHIZOMA RHEI (TK)

✓ RHAPONTICA SECTION:

✓ *R. rhaponticum*

✓ *R. compactum*

✓ *R. undulatum*

✓ *R. ribes*

RHIZOMA RHEI (TK)

- *Rheum palmatum* var. *tauguticum* --- North China
- *R. officinale* ----- South China
- Drug obtained from these plants are known as Chinese Rhubarb
- In dried Chinese Rhubarb;
- **Total anthracene ----- %3-5**
- **Tannoids (Catechol, glucogallin)-----%5**

RHIZOMA RHEI (TK)

- Free anthraquinones %0.1-0.2;
- Crysophanol (C3 → CH₃)
- Emodin (C3 → CH₃; C6 → OH)
- Physcion (C3 → CH₃; C6 → OCH₃)
- Aloe-emodin (C3 → CH₂OH)
- Rhein (C3 → COOH)

RHIZOMA RHEI (TK)

- Glycosides : Major compounds
- Anthraquinone glycosides
- Anthranol ve anthrone glycosides
- Polymer compounds:
- Sennidine A and B ----- Direin anthrone
- Palmidin A,B,C --- Heterodianthrone (emodin+ crysophanol)

RHIZOMA RHEI (TK)

➤ USES

- Low Dosage (50-100 MG) --- ASTRINGENT
- High Dosage (500MG-2 G) --- LAXATIVE, PURGATIVE
- Not irritant; elderly and children can use.

RHIZOMA RHEI (TK)

- ✓ *Rheum rhaponticum* ----- English Rhubarb
- ✓ India; Europe → ornamental plant
- ✓ Rhizomes contain less active ingredients → %1-3
- ✓ Free anthraquinones → Crysophanol, Emodin

RHIZOMA RHEI (TK)

✓ Rhaponticoside ----- estrogenic glycoside

✓ Used as rhubarb; 2-4 times less effective than Chinese rhubarb

RHIZOMA RHEI (TK)

❖ *Rheum ribes* (Işgın):

- ❖ The unique *Rheum* species from Turkey
- ❖ East Anatolia → Van, Elazığ
- ❖ Petiols are used as vegetable
- ❖ Anthracene derivatives ve tannins
- ❖ Traditionally used as astringent

RHIZOMA RHEI (TK)

- Anatomic properties:
- Star hilum in transverse section of cambium is specific
- Relatively large (50-120 μ) calcium oxalate cluster crystals also specific
- These properties help to identify the drug easily

CORTEX FRANGULAE (Ph.E) Alder buckthorn, Barut Ağacı

- *Rhamnus frangula* (Rhamnaceae)
- Dried barks of the trunk and branches
- Grows in Medium and South Europe
- In Turkey; North and Medium Anatolia, Trabzon, İstanbul, Bolu, Ankara, Bursa

CORTEX FRANGULAE (Ph.E) (BARUT AĞACI)

- Drug obtained from Poland, Czech Republic, Yugoslavia and Russia
- This drug should be used a year after it is collected or after dried in 100°C for an hour.

CORTEX FRANGULAE (Ph.E) (BARUT AĞACI)

- Outer layer of the barks is dark grey coloured, has white ellipsoid lenticels; inner layer is yellow-orange coloured
- Rows of druse crystal are specific for the identification of the drug
- Anthracene derivatives → 2-4%
- Free anthraquinones → 0.05-0.1% (Crysophanol, Emodin)

CORTEX FRANGULAE (Ph.E) (BARUT AĞACI)

- As anthracene glycosides;
- Glucofranguloside----Emodin+ Rh+Gl (from -OH in 1. or 8. C positions) (Primary glycoside)
- Franguloside-----Emodin+Rh (Secondary glycoside)
- Emodin dianthrone → Dimeric structure
- Heterodianthrone (emodin+crysophanol)—PALMITIN C

CORTEX FRANGULAE (Ph.E) (BARUT AĞACI)

GLUCOFRANGULOSIDE (PRIM.
GLY.)

EMODIN DIANTHRONE

PALMITIN (HETERODIANTHRONE)

CORTEX FRANGULAE (Ph.E) (BARUT AĞACI)

- The drug can be used in Decoction or Liquid extract forms or in powdered form
- Acts as Laxative - Purgative

CORTEX RHAMNI PURSHIANAE (TF), Cascara Sagrada, Cascara Buckthorn (Ph.E.)

- *Rhamnus purshiana* (Rhamnaceae)
- Dried barks of young trunk and branches
- American plant, cultured in Kenya
- The drug is obtained between April-August and dried in shadow
- The drug should be used a year after it is collected or after drying an hour in 100°C

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- The drug is typically more or less covered with lichens
- The drug consists of rather thick fragments (2-4 mm), cut into 10-20 cm strips, grey coloured with lenticels on the outer surface
- Powdered drug consists of sclereids and basic series of Ca-oxalate crystals

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- 4-5% Anthracene derivatives:
- Free Anthraquinones → 0.2-0.8% (Crysophanol, Emodin, Aloe-emodin)

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- O-Glycosides:
- Emodin-oxanthrone glycoside
- Emodin-anthrone glycoside

Emodin-oxanthrone glycoside

Emodin-anthrone glycoside

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- C-Glycosides:
- Aloin (Aloe-emodin antron glycoside)
- Chrysaloin (Chrysophanol anthrone glycoside)

Aloin (Aloe-emodin antron glycoside)

Chrysaloin (Chrysophanol anthrone glycoside)

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- Primary Glycosides:
- Cascaroside A (Aloin's primary glycoside) (+)
- Cascaroside B (Aloin's primary glycoside) (-)

CORTEX RHAMNI PURSHIANAE (TF), CASCARA SAGRADA (Ph.E.)

- Cascaroside C (Krizaloin's primary glycoside) (+)
- Cascaroside D (Krizaloin's primary glycoside) (-)
- Glycosidic bonds from 1. and 8. positions
- Powder (250 mg-1g)
- Used as laxative, purgative

FRUCTUS RHAMNI CATHARTICAE

Akdiken Meyvesi, Buckthorn Fruit (TK)

- Mature fruits of *Rhamnus cathartica* (Rhamnaceae)
- Fruits are in 6-8 mm diameter, drupa, collected in September-October
- Grows in South Europe, North Africa, Mediterranean
- In Turkey; Abant, Trabzon

FRUCTUS RHAMNI CATHARTICAE AKDİKEN MEYVESİ (TK)

- Anthracene amount → 0.7-1.4 %
- Anthracenes mainly found in seeds, less in pulp
- -Emodin
- -Franguloside (Emodin 6-O-rhamnoside)
- -Emodin-anthranol glycoside

FRUCTUS RHAMNI CATHARTICAE AKDİKEN MEYVESİ (TK)

- Flavonoids are found in Pulp
- Flavonol derivatives:
- Kaempferol and Quercetin derivatives

Kaempferol

Quercetin

FRUCTUS RHAMNI CATHARTICAE AKDİKEN MEYVESİ (TK)

- Catharticoside → Methylether of kaempferol
- Fruit juice (doesn't contain Anthracene)----diuretic due to Flavonols
- Fruit----- acts as laxative, purgative; used in veterinary

Rhamnus petiolaris, Buckthorn, Boyacı Dikeni, Cehri

- Grows in Turkey; Exported
- Fruits of the plant growing in Kayseri consists of 4% fixed oil and 0.08-0.15% free anthracenes

Rhamnus petiolaris, Buckthorn, Boyacı Dikeni, Cehri

- Barks:
- - Free anthraquinones 0.12 %
- Emodin, PhyscionFiskiyon, chrysophanol
- -Heterozit %0.9
- Emodol, physcion, krizofanol glycosides

Rhamnus petiolaris, Boyacı Dikeni, Cehri

- Fruits was once used as purgative, not anymore
- Contains a yellow colouring compound → used as yellow dye for fabrics and oils
- Over 20 *Rhamnus* species are growing in Anatolia; fruits and barks of some of these species are used as purgative

FOLIA SENNAE (TK) Sinameki Yaprağı, Senna leaves (Ph.E.)

- Dried leaves of some *Cassia* (Leguminosae/Fabaceae) species
- Grows in North Africa, semi-desert and mountains of Arabia
- Drug is obtained from:
 - *Cassia angustifolia* (Arabia)-----Folia Sennae tinnevelly (Tinnevelly senna)
 - *Cassia acutifolia* (Tropical Africa)-----Folia Sennae alexandrina (Alexandrian senna)

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Folia Sennae Tinnevelly;
- Leaves are of 3-5 cm, yellowish-green, glabrous
- This drug is marketing in Turkey
- Folia Sennae Alexandrina;
- Leaves are of 2-4 cm, greyish-green, both layers are pubescent

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Fruits of these plants are also used as drug, named as *Fructus Sennae*
- *Folia Sennae*

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Both leaves and fruits contain anthracene derivatives 2-3%
- -Free Anthraquinones:
- Rein (0.05-0.10%)
- Chrysophanol, Emedin
- -Glycosides: Found in Leaves;
- Sennoside A and B---acid hydrolysis---Sennidin A and B (Direinanthrone)+2 mol Gl.

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Sennidin A-----d
- Sennidin B-----optically inactive

Sennoside A and B (Direinanthrone

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Sennoside C and D---acid hydr.---Sennidin C and D
(Heterodianthrone----aloe-emodin+rein) + Gl+Gl

Sennoside C and D (heterodianthrone→aloe-emodin+rein)

Doç. Dr. Sinem Aslan Erdem

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Fruits;
- Sennoside A and B
- Glucosennoside A and B (Primary glycoside)

- Leaves also contains a kind of irritant resin
- Leaves can be get rid of this resin by washed with 95°Ethanol (resin will be removed at ¼ ratio)

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- Resin ----irritant to uterus ve bladder
- Fruits must be used after removal of the irritant seeds
- Drug is used as laxative and purgative in forms of powder, infusion or enema

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

ENEMA:

- F.Sennae-----15g
- Na₂SO₄-----15g
- Water -----500g

INFUSION:

- 5-10g senna leaves + 200 ml boiled water → wait for 5' → filter and drink

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- **Senoside A and B (10-40mg)----Used as Laksative-Purgative**
- *Cassia alata*, *C. aphylla*, *C. fistula* ve *C. nigricans* species also can be used for the same purposes; especially *C. fistula* is used for children as a mild, pain-free purgative in form of 5% infusion

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

PREPARATIONS

- ROHA-LAX-----Sennoside A (tablet, granule)
- SENOKOT-----Sennoside B
- TİLAX-----F.Sennae +Fr. Coriandri+Fr. Anisi
- + R.Liquiritiae
- X-M-DIET SOLÜSYON---Sennoside A+B Calcium (150mg)
- Purgative----- Sennoside A+B kalsiyum (300mg)

FOLIA SENNAE (TK) SİNAMEKİ YAPRAĞI (Ph.E.)

- X-M-SOLÜSYON-----Sennoside A+B kalsiyum
- BEKUNİS-----Sennoside
- AGİOLAX (Granül)-----Plantago ovata seeds
Plantago ovata seed coat
Sinameki fruit
- KARBOSEPTİN (Tablet)----- Carbo Ligni
Soufre depuratum
Senna yaprağı
Rh. Rhei extract
Fenolftalein

FRUCTUS CASSIAE FISTULAE

- Mature fruits of *Cassia fistula*
- India and tropical regions
- Pulp of the fruit is used as drug

FRUCTUS CASSIAE FISTULAE

- Pulp;
- Pectin , musilage and sugars → 50%
- 1-3% → Anthracene derivatives
- Among free anthracenes REIN is the most abundant
- SENNOSIDE A and B
- Laxative in 5-10g doses

ALOE (TF) SARISABIR

- Aloe is a juice, obtained from leaves of various *Aloe* (Liliaceae) species.
- *Aloe ferox* (*A. lucida*)-----South Africa
- Dentate leaves, flowers are red
- *Aloe vera* (*A. Barbadosense* = *A. vulgaris*)---North Africa
- Dentate leaves, flowers are yellow

ALOE (TF) SARISABIR

❖ *Aloe ferox* - *Aloe lucida* (Cape Aloes):

❖ The juice is concentrated by boiling. Greenish-yellow coloured

➤ *Aloe vera* - *Aloe hepatica* (Curacao Aloes/Barbada Aloes):

➤ The juice is self-concentrated; dark coloured, opaque

ALOE (TF) SARISABIR

- Anthrasenosides 15-30%
- **ALOIN (=Barbaloin) (Barbada Aloes → 15-30%) , (Cape Aloes → 15-20%)**

ALOE (TF) SARISABIR

- ALOIN (Aloe-emodin C-glycoside)----oxidant hydrolysis by Na periodate or $\text{FeCl}_3 \rightarrow \text{Aloe-emodin} + \text{Gl.}$
- Free Anthraquinones 0.05-0.5%
- Aloe-emodin

ALOE (TF) SARISABIR

- Resin 10-20% (Anthracene polymer)
- Resin is irritant for uterus. Not used in pregnant and hemorrhoid patients
- Purgative → acts on large bowel
- Pilule form 100 mg doses----laxative
200-500 mg doses---purgative

ARARROBA, Goa Powder, Goa Tozu

- *Andira araroba* (Fabaceae)
- A tree from Brazilian forests
- **Yellow powder found in schizolysigenous secretory pockets**
- Anthrone, Anthranol and related compounds → Chrysarobin
- Drug → Evaporated hot benzene extract of powder

ARARROBA, Goa Powder, Goa Tozu

- Antiseptic and antiparasitic.
- Usage; skin disorders especially psoriasis

RADIX RUBIAE, BOYACI KÖKÜ

- *Rubia tinctorium* (Rubiaceae) common madder, dyer's madder
- Dried underground parts
- Southwest Europe
- A dye obtained from the roots---known as "Edirne Kırmızısı" or "Türk Kırmızısı"

RADIX RUBIAE, BOYACI KÖKÜ

- Colouring compounds → Anthraquinones which contain -OH groups in 1st and 2nd positions
- These compounds:
- Alizarin----1,2 dihydroxyanthraquinone

RADIX RUBIAE, BOYACI KÖKÜ

- Purpurin---1,2,4 trihydroxyanthraquinone

RADIX RUBIAE, BOYACI KÖKÜ

- Ruberythric acid---alizarin glycoside (alizarin+Gl+xyl)

Ruberythric acid

COCCIONELLA, Cochineal

- Dried female insect, *Coccus cacti* (Coccidae)
- They are especially found on a cactus named *Opuntia coccinelifera* (Cactaceae); in Mexico and Peru regions
- Insects are brushed from plants; insects are killed by water vapor, ether vapor or sulphur fumes; dried under sunlight or in oven at 40°C

COCCIONELLA

- Insects contain 10% carminic acid

Carminic acid

HERBA HYPERICI, St. John's Wort, Sarı Kantaron

- Flowered branches of *Hypericum perforatum* (Hypericaceae) taze
- A European plant
- Widely distributed in Turkey
- Leaves are coated with many glandular hairs ; when the leaves are held in the light oil droplets are seen as bright spots.

HERBA HYPERICI, SARI KANTARON

- -DIANTHRON structured compounds:
- Hypericines
- Hypericine----hexahydroxydimethylnaftodianthrone
- Isohypericine
- Pseudohypericine
- Protohypericine

HERBA HYPERICI, SARI KANTARON

Hypericine
(emodindianthrone)

Isohypericine
(emodindianthrone)

HERBA HYPERICI, SARI KANTARON

Protohypericine
(emodindianthrone)

Pseudohypericine
(emodindianthrone)

HERBA HYPERICI, SARI KANTARON

- Hypericine is not purgative
- Used in fatigue and mental depression as tonic and stimulant.
- It is a Photosensitive compound

HERBA HYPERICI, SARI KANTARON

St. John's wort oil (Kantaron yağı)

- Flowered branches are allowed to stand in olive oil for 15 days; filtered and used.
- Traditionally used in wound healing
- *Essential oil of H. perforatum* ---- antihelmentic

HERBA HYPERICI, SARI KANTARON

- There are about 70 *Hypericum* species growing in Turkey
- Species used traditionally:
 - *H. calycinum*
 - *H. empetrifolium*
 - *H. tetrapterum*
 - *H. triquetrifolium*
 - *H. scabrum* (Yozgat)
 - *H. heterophyllum* (Ankara)

HERBA HYPERICI, SARI KANTARON

- German Comission A recommends for anxiety, depressive moods, skin inflammations, wound and burns
- Standardized extract of the drug is used in 300 mg doses for depression 3 times in a day.