Pharmacognosy and Phytochemistry

Glycosides-Part 2

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to explain

- Anthraquinone Glycosides
    - **Cascara**
    - **Rhubarb**
    - **Senna**
    - **Aloe**
    - **Carmine**
    - **Hypericin**

Objective

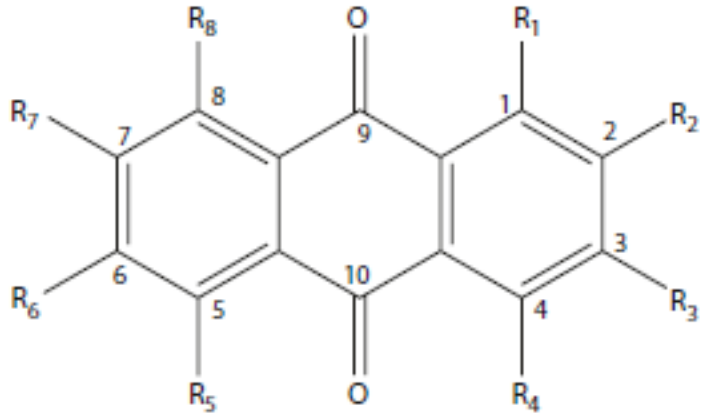
The objective of this course is to give to the students of pharmacy the basic knowledge about the Glycosides as major phytoconstituents.

Anthraquinone Glycosides

- They are glycosides having their aglycone moieties closely related to anthracene.
- They are present in noticeable amounts in a variety of drug substances.

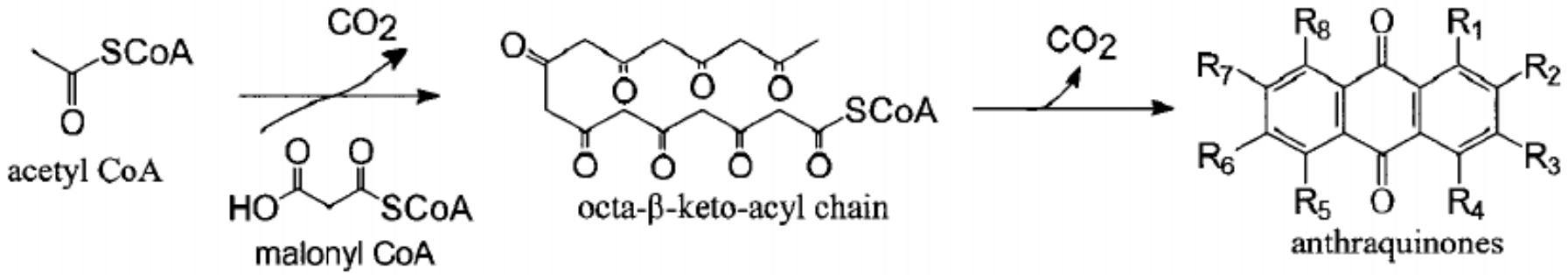
  Examples: Aloe, cascara, and senna.
- These drugs are invariably employed as stimulant cathartics, and exert their action by increasing the tone of the smooth muscle in the wall of large intestine.
- The free anthraquinone aglycones exhibit therapeutic activity.
- The sugar residue facilitates absorption and translocation of the aglycone to the site of action.

General Anthraquinone
Structure
with numbering



Anthraquinones: Biosynthesis

- The biosynthesis of all secondary metabolites have revealed the existence of 3 very important biosynthetic routes: 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, then form the malonyl Co enzyme A by the addition of another acetate unit.
- Likewise, the octa-β keto methylene chain undergoes simultaneous loss of CO_2 and cyclization gives anthraquinones.



Cascara sagrada

- The name ‘cascara sagrada’ is Spanish for the sacred bark.
- **Synonym**: Purshiana bark; Persian bark; Cascara bark.
- **Biological Source**: *Cascara sagrada* is the dried bark of *Rhamanus purshiana* belonging to the family: Rhamnaceae.
- It is usually collected **at least one year** prior to its use.

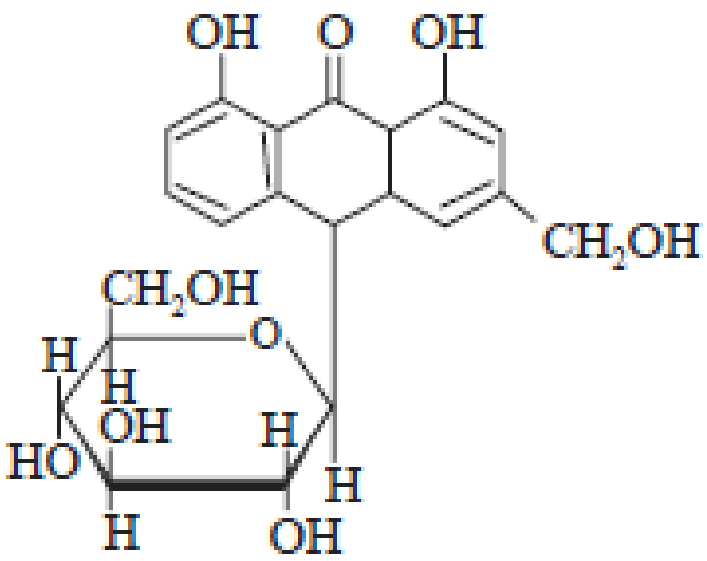
The **chemical constituents**: The cascara sagrada bark is found to contain two major types of anthracene compounds, namely:-

(a) Normal O-Glycosides These are based on *emodin-like* structures and constitute about **10 to 20**% of the total glycosides

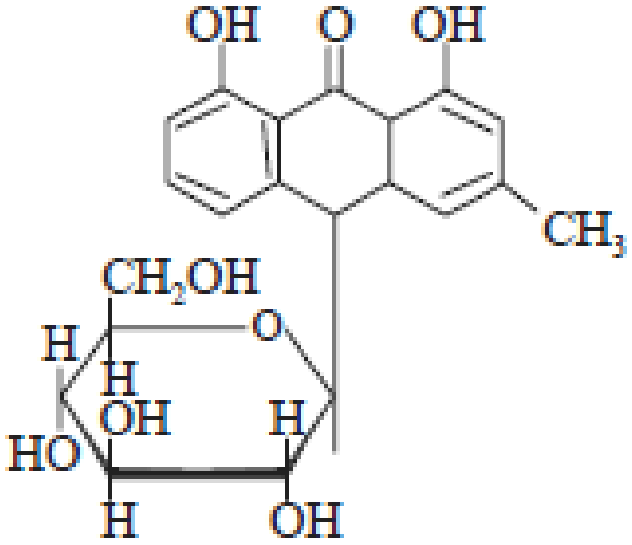
(b) *Aloin-like* C-Glycosides: These comprise of about **80 to 90**% of the total glycosides.

The two C-glycosides are known as barbaloin and deoxybarbaloin.

Cascara sagrada



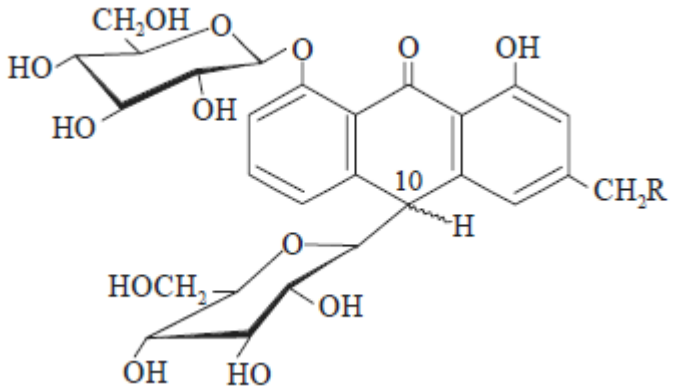
Barbaloin (Aloin)



Deoxybarbaloin (Chrysaloin)

- The main active constituents are four glycosides usually designed as Cascarosides-A, B, C and D.
- Cascarosides A and B are optical isomers of barbaloin ; whereas cascarosides C and D are optical isomers of deoxy-barbaloin.

Cascara sagrada



Uses:-

Laxative, purgative

Glycosides	Type	R	Configuration
CASCAROSIDE	A	OH	(10 S)
CASCAROSIDE	B	OH	(10 R)
CASCAROSIDE	C	H	(10 S)
CASCAROSIDE	D	H	(10 R)

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

Upon drying, they are Oxidized to

Reduced forms → anthraquinones

(Anthrone and anthranol) (less active)

Rhubarb

Biological Source: Rhubarb is the rhizome and roots of *Rheum officinale*, belonging to the family *Polygonaceae*.

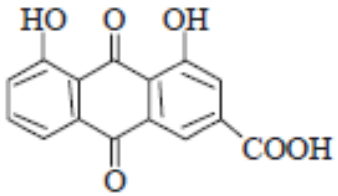
Chemical Constituents: Rhubarb essentially contains the anthraquinone glycosides and the astringent components.

The former range between 2 to 4.5% and are broadly classified into four categories as stated below:

(a) Anthraquinones with —COOH moiety
(b) Anthraquinones without —COOH moiety
(c) Anthrones and Dianthrones of Emodin
(d) Heterodianthrones

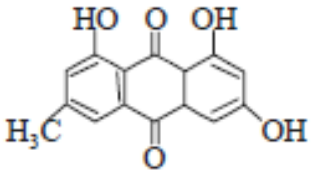
Rhubarb

(*a*) **Anthraquinones with —COOH moiety**—*e.g.*, Rhein; Glucorhein;

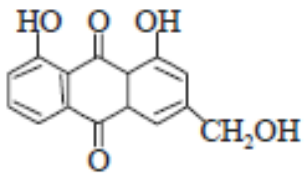


Rhein

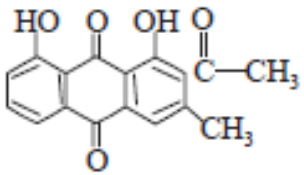
(*b*) **Anthraquinones without —COOH moiety**—*e.g.*, Emodin; Aloe-Emodin; Chrysophanol; Physcion;



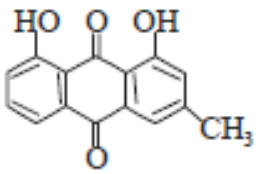
Emodin



Aloe-Emodin

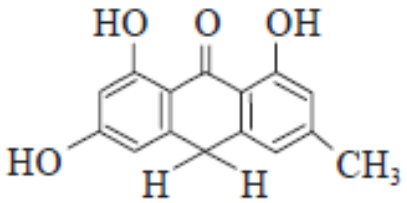


Chrysophanol

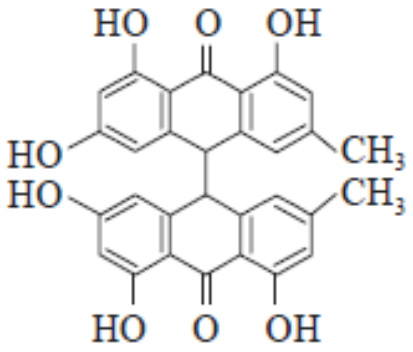


Physcion

(*c*) **Anthrones and Dianthrones of Emodin**—as shown below:



Emodine Anthrone



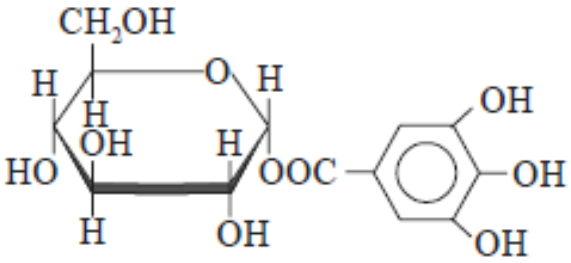
Emodin Dianthrone

Rhubarb

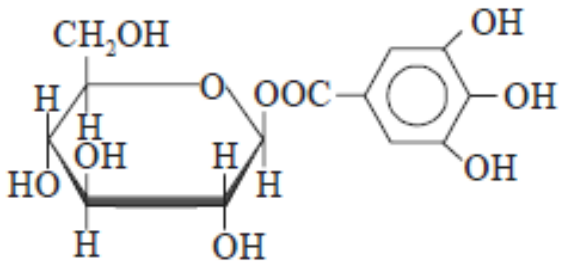
Heterodianthrones—e.g. Palmidin A, B, and C, which are produced from two different anthrone molecules, as stated under:

Palmidin A : Aloe-emodin anthrone + Emodin anthone
Palmidin B : Aloe-emodin anthrone + Chrysophanol anthrone
Palmidin C : Emodin anthrone + Chrysophanol anthrone

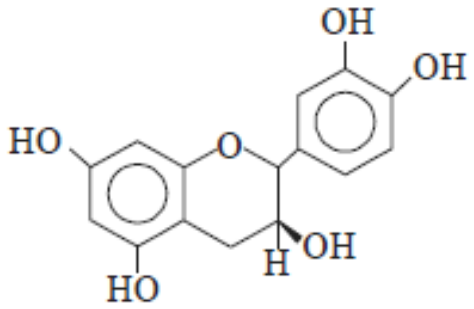
However, the astringet portion of rhubarb chiefly comprises with the following components, namely: **gallic acid** as *α- and β-glucogallin*; **tannin** as *d-catechin* and *epicatechin*.



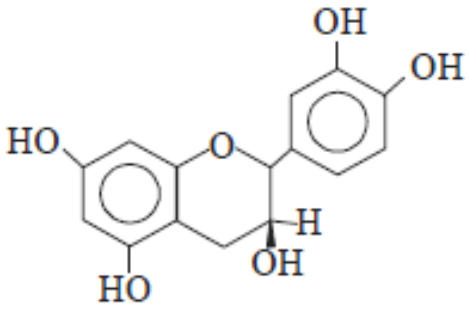
α-Glucogallin



β-Glucogallin



d-Catechin



Epicatechin

Rhubarb

- Rhubarb also consists of rheinolic acid, pectin, starch, fat and calcium oxalate.
- The calcium oxalate content ranges between 3-40% in various species of rhubarb which reflects directly on the corresponding ash values (i.e., total inorganic contents).

Uses:-

1. It is used mainly in the form of an ointment in the treatment and cure of chronic eczema, psoriasis, and trichophytosis-as a potent keratolytic agent.
2. It is employed as a bitter stomachic in the treatment of diarrhoea.
3. It is also used as a purgative.

Senna

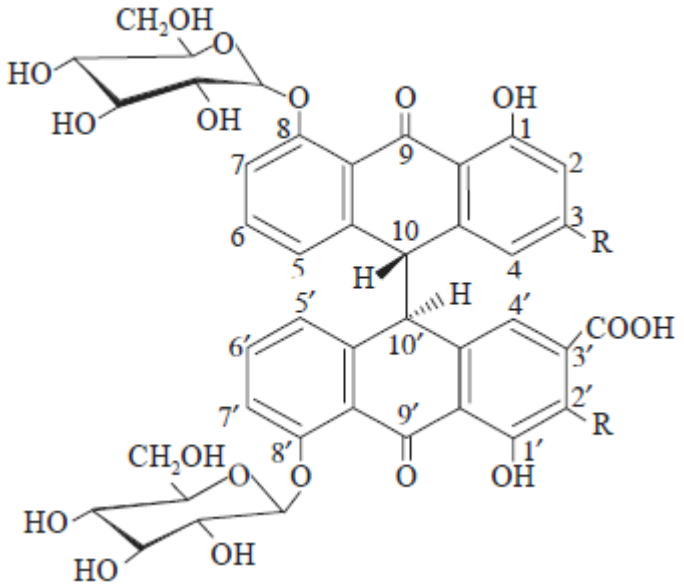
- ✓ Senna was first used in the European medicine as early as the 9th or 10th century by the Arabs.

- ✓ **Biological Sources**: Senna is the dried leaflets of
  Cassia acutifolia (Alexandria senna)
  (or)
  Cassia angustifolia (Indian or Tinnevelley Senna)
- ✓ Family: Leguminoseae.

C. acutifolia grows wild in the vicinity of Nile River (Egypt) extending from Aswan to Kordofan; whereas, *C. angustifolia* grows wild in the Arabian Peninsula, Somalia, India, and Northwest Pakistan.

Phytoconstituents present in Senna

The principle active constituents of senna are four sennosides A, B, C and D, which are the dimeric glycosides.

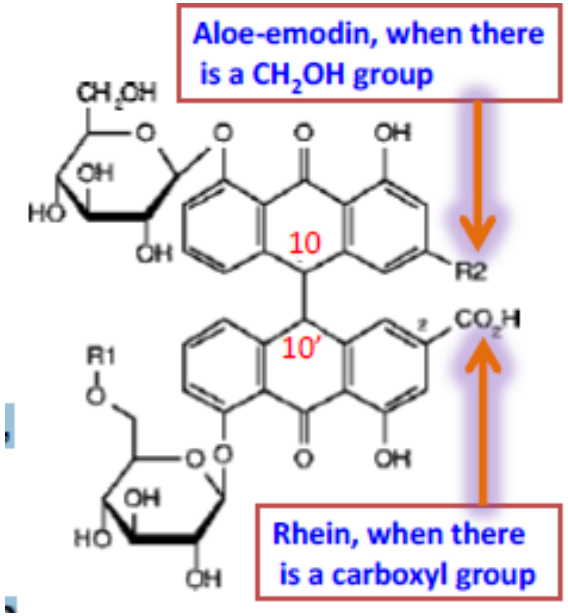


Glycosides	R	C-10 & C-10'	Characteristics
Sennoside-A	—COOH	*trans-*	Optically active, a levoratory isomer present in large concs; water insoluble
Sennoside-B	—COOH	*meso-*	Intramolecularly compensated present in large concs; more water soluble
Sennoside-C	—CH_2OH	*trans-*	Aglycone (–) isomer; present in small concs;
Sennoside-D	—CH_2OH	*meso-*	Aglycone (+) isomer; present in small concs.

Phytoconstituents and Formulations of Senna

Sennoside A and B, are homodianthrones and have their aglycones as rhein.

Sennoside C and D, are heterodianthrones and have their aglycones as rhein and aloe-emodin.



Uses and Mechanism of action of Senna

- Senna and its branded preparations, for instance: GlaxennaR (Glaxo); Pursennid(R) (Sandoz); are usually employed as purgative in habitual constipation.

- The glycosides are first absorbed in the small intestinal canal after which the aglycone portion gets separated and ultimately excreted in the large intestine (colon).

- The released anthraquinones irritate and stimulate the colon thereby enhancing its peristaltic movements causing bulky and soft excretion of faces.

- The inherent action of senna is associated with appreciable griping , and therefore, it is generally dispensed along with carminatives so as to counteract the undesired effect.

Aloe

- ✓ **Biological Sources**: Aloe is the dried latex of leaves of various species of Aloes, namely:
- ✓ *Aloe barbadensis* (**Curacao** Aloe)
- ✓ *Aloe ferox* (**Cape** Aloe)
- ✓ *Aloe perryi* (**Socotrine** Aloe)
- ✓ *Aloe Juvenna* (**Zanzibar** Aloes)

Aloe vera (barbadensis)

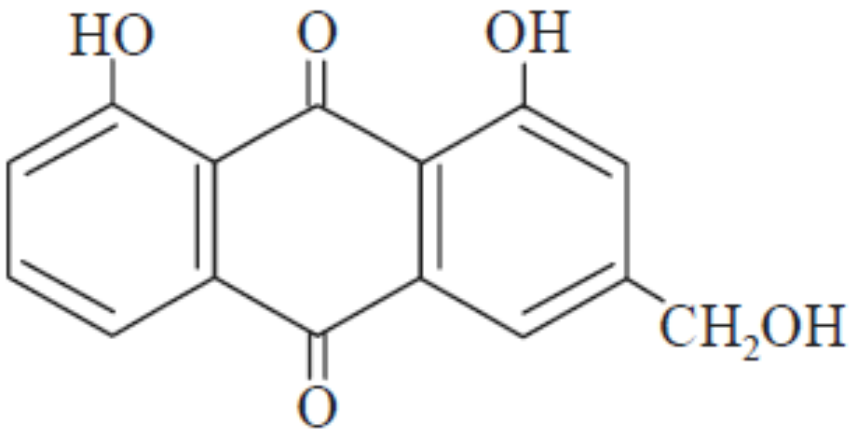
Aloe ferox

S. No.	Properties	Curacao Aloes	Cape Aloes	Socotrine Aloes	Zanzibar Aloes
1.	**Colour**	Brownish black opaque mass	Dark brown or greenish brown to olive brown mass	Brownish yellow opaque mass	Liver brown colour
2.	**Odour**	Strong odour resembles with *Iodoform*	Sour and distinct odour	Unpleasant odour	Characteristic but agreeable odour
3.	**Taste**	Intense bitter taste	Nauseating and bitter taste	Extremely bitter and nauseous taste	Bitter taste
4.	**Texture**	Waxy and somewhat resinous	Breaks with a glassy fraction	Fractured surface looks conchoidal	A dull, waxy, smooth and even fracture

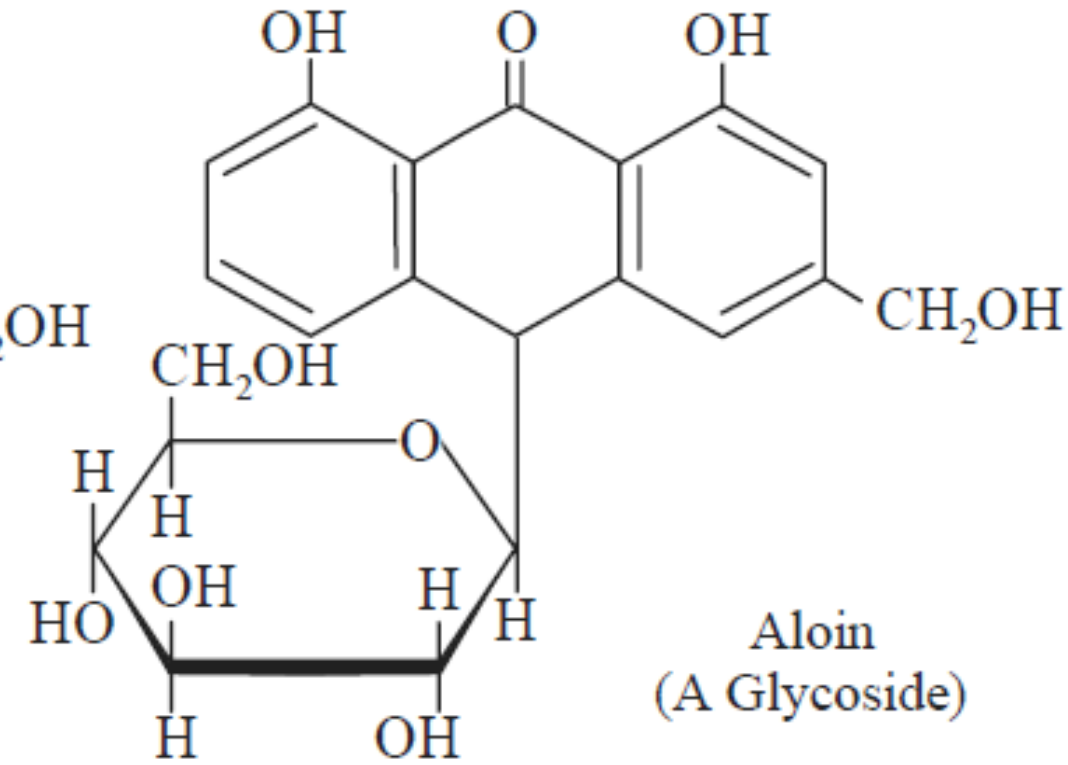
Aloe Perryi

Aloe: Phytochemical constituents

- ✓ Aloe-emodin occurs in the free state and as a glycosides in various species of Aloe and also in Rheum (Rhubarb).
- ✓ **Curacao aloes** contains about two and half times the amount of aloe emodin when compared to **cape-aloes**.



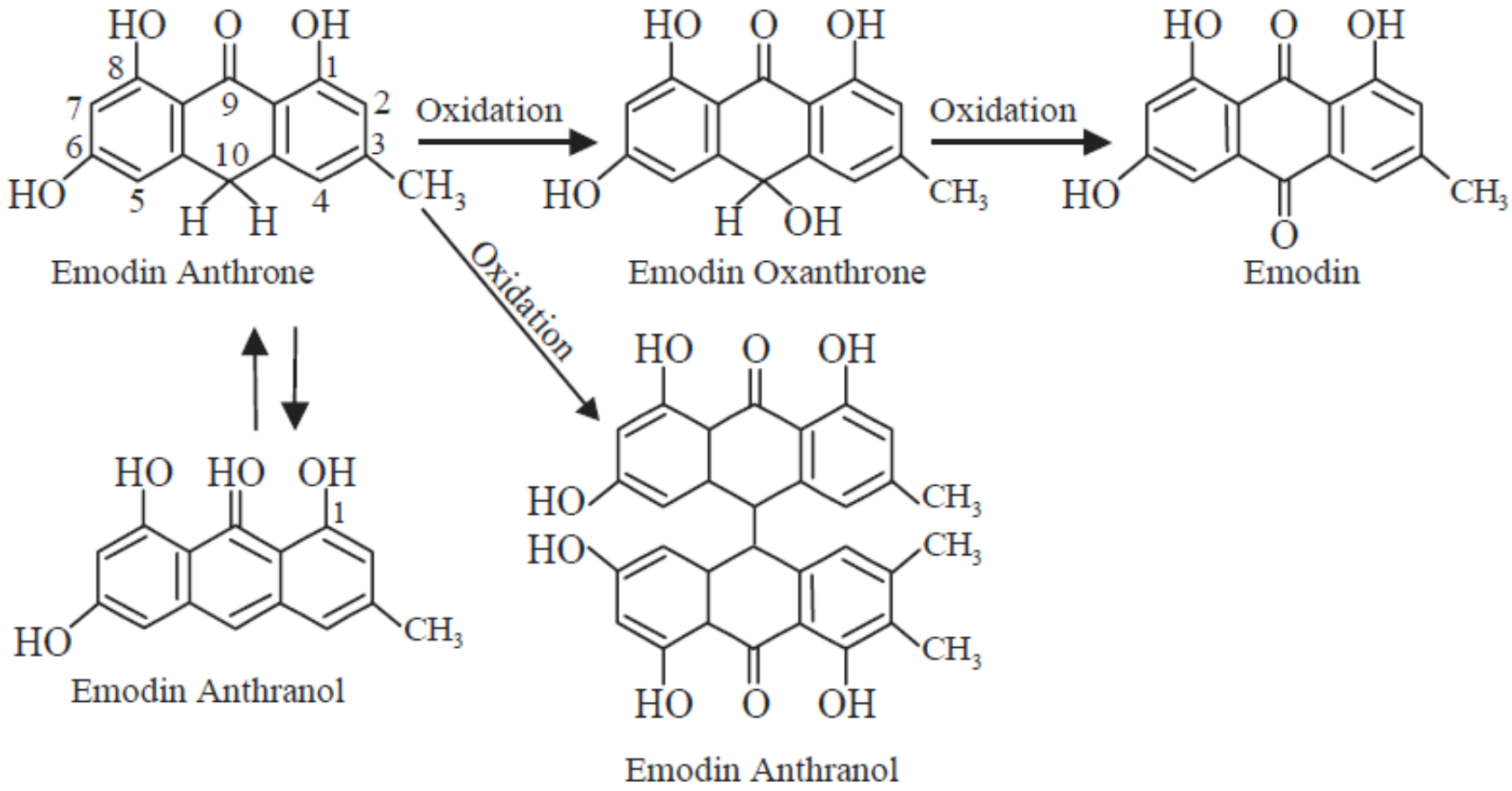
Aloe-Emodin
(Free State)



Aloin
(A Glycoside)

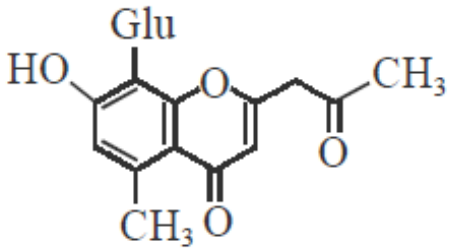
Structural Relationship of Emodin

The glycosides of anthranols, dianthrones, and oxanthrones i.e., the reduced derivatives of anthraquinones, invariably found in various plant substances.

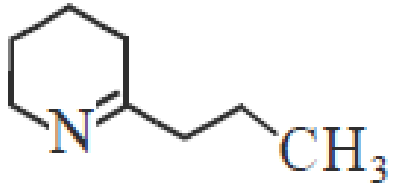


Aloe: Phytochemical constituents

- ✓Besides, aloin (or barbaloin), the aloes also contain isobarbaloin (Curacao aloes), b-barbaloin) = (Cape aloes), aloe emodin and resins.
- ✓The principal resin present in the aloes is known as aloesin.
- ✓γ-Coniceine, which is a piperidine alkaloid is found in *Aloe gililandii*, *A. ballyi*, and *A. ruspoliana* (Family: Liliaceae).



Aloesin



γ-Conieceine

Aloe: Uses

1. Aloes and aloin are official drugs, and used as a **purgative** by exerting its action mainly on colon.
2. Aloes find its usefulness as an external aid to painful inflammatory manifestations.
3. It constitutes an important ingredient in the ‘Compound Tincture of Benzoin’
4. Aloe gel made from the mucilaginous latex of *A. vera* is frequently employed in the treatment and cure of radiation burns to get immediate relief from itching and pains.
5. Aloe usually causes gripping and is, therefore, administered along with carminatives.

Carmine

- ✓ Carmine, also called cochineal (when it is extracted from the cochineal insect: *Dactylopius coccus; Family: Coctaceae*), cochineal extract, crimson lake, or carmine lake – is a pigment of a **bright-red** color obtained from the aluminium complex derived from **carminic acid**.
- ✓ Specific code names for the pigment include natural red 4, C.I. 75470, or E120. Carmine is also a general term for a particularly **deep-red color**.

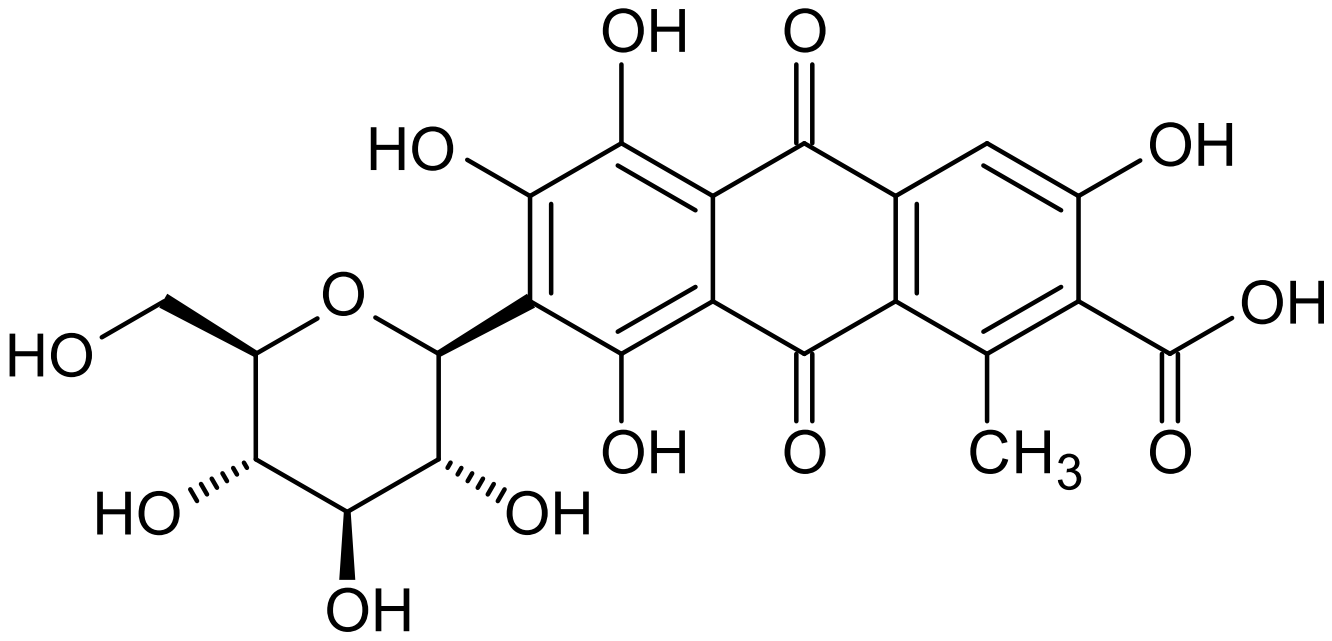
Cochineal insect

Uses:-

Carmine is used as a colouring agent for lipstick, confectionaries, beverages.

Carmine

Carminic acid



Hypericin

- **Hypericin** is a naphthodianthrone, an anthraquinone derivative, together with **hyperforin**, is one of the principal active constituents of *Hypericum*.
- **Botanical Name: *Hypericum perforatum***
- **Family**: ***Hypericaceae***
- It is also called as **St. John's Wort** because it flowers around **St. John's day** and **wort** is an **Old English** term for a **plant**.
- **Habitat**: is native to parts of Europe and Asia but has spread worldwide including India, China, Canada, Africa, and the United States.
- **Composition:** Contains at least 10 substances including **hypericin** & **hyperforin**, which are shown to have biological activity.

Leaves are used **for antidepressant** and other purposes;

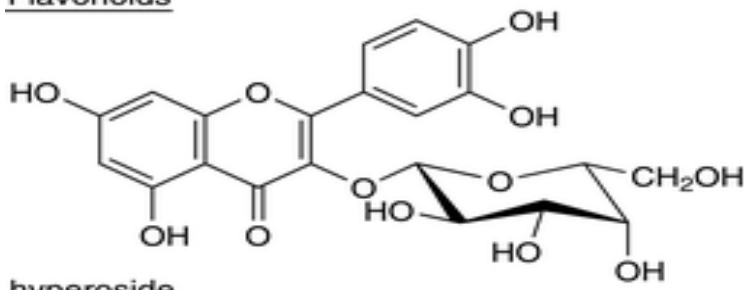
Flowers are used **to promote wound healing**

Chemical Constituents

- Substances found and described using various chromatographic methods (esp. HPLC).
- Flavonol derivatives
- Biflavones
- Proanthocyanidines
- Xanthones
- Phloroglucinols*
- Naphthodianthrones*

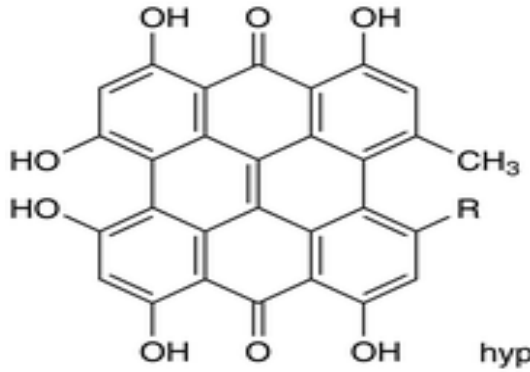
Most notable: hypericin** and **hyperforin

Flavonoids



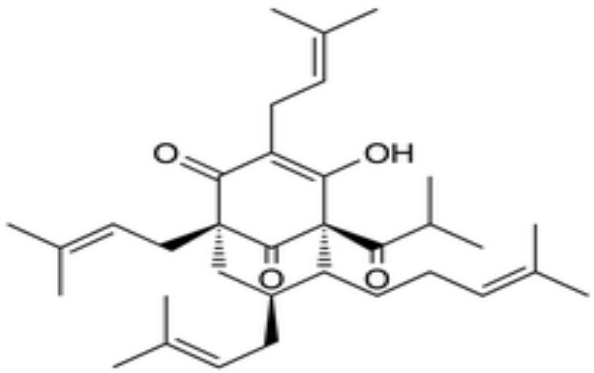
hyperoside

Dianthrones



	R
hypericin	CH_3
pseudohypericin	CH_2OH

Prenylated phloroglucinols



hyperforin

Hypericin/ St John's Wort (SJW)

Uses:-

- Treatment of mild to moderate depression.
  #1 Anti-depressant in Germany
- Relieves anxiety, insomnia, and headaches.
- **Dosage**: Daily dose of **900 mg of SJW extract** (standardized to **0.3% hypericin**) found to be equivalent to 20 mg fluoxetine
- **Doses up to 1800 mg tolerated in severe depression**

Traditional Uses:-

- Anti-inflammatory, Sedative, Diuretic, Anti-malarial
- Used on first degree burns and healing of other wounds.

Adverse Effects:-

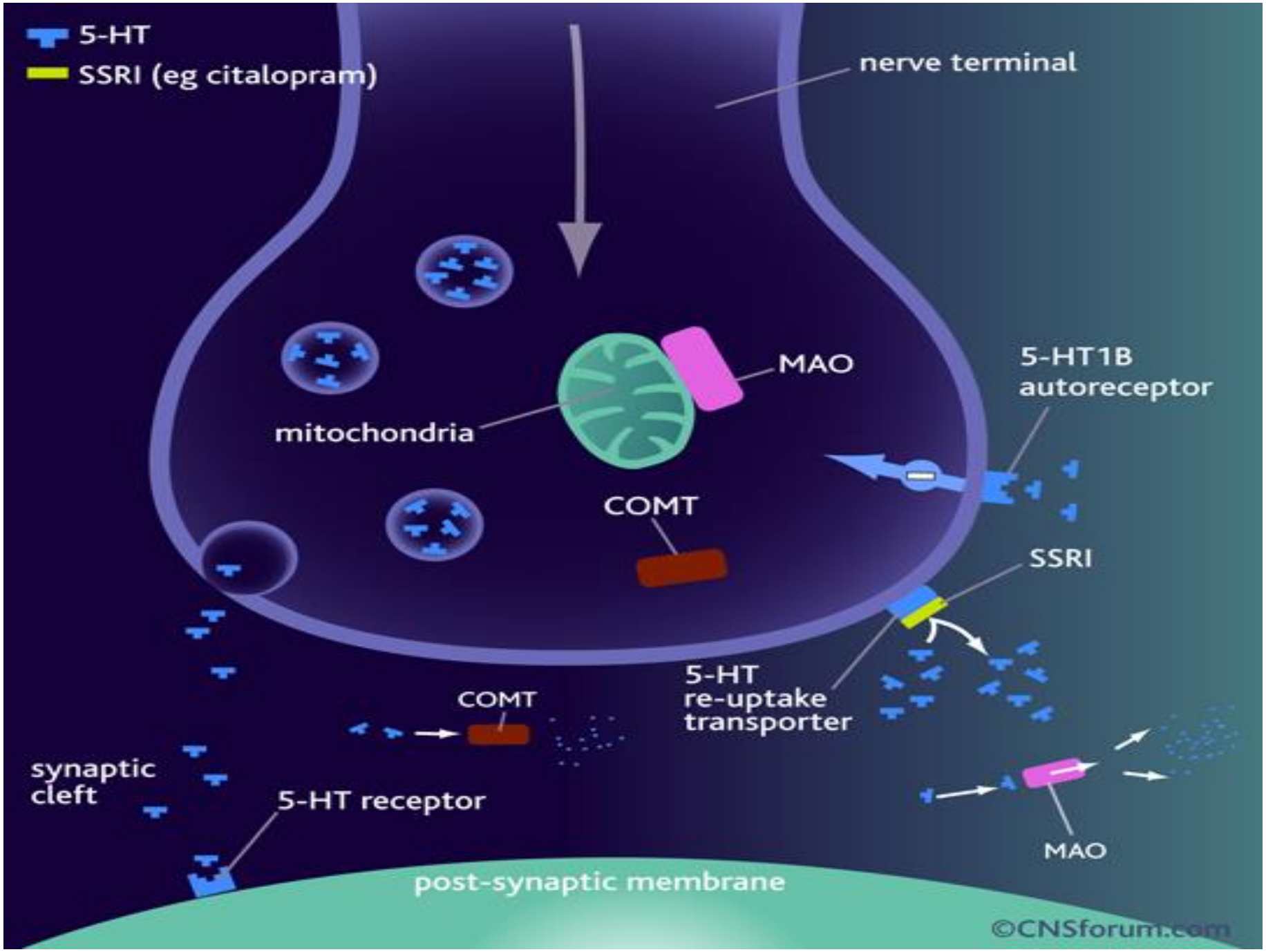
- **Sun-exposure:** Photosensitivity/Phototoxicity
- Insomnia, vivid dreams, headache, dizziness, nervousness, sexual dysfunction, GI upset and fatigue.

Mechanism of action

Depression is caused by a deficiency of serotonin (5HT, 5-Hydroxytryptamine) or norepinephrine.

Mechanism of action of SJW:-

- **Reuptake inhibition of monoamines** (specifically, serotonin, norepinephrine, and dopamine).
- **Monoamine oxidase inhibitors (MAOIs):** There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. **MAO inhibition occurs** with high concentrations **of SJW**.
- Causes **up-regulation of 5-HT_2 receptors**.
- These effects exerted by a combination of **hypericin** and **hyperforin**.


5-HT
SSRI (eg citalopram)
nerve terminal
MAO
5-HT1B
autoreceptor
mitochondria
COMT
SSRI
5-HT
re-uptake
transporter
COMT
synaptic
cleft
5-HT receptor
MAO
post-synaptic membrane
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Herb-drug interactions of Hypericin with the following medications:-

HIV Medications: Reduced blood levels with possible loss of HIV suppression

Warfarin: Reduced anticoagulant effects and need for increased dose

Cyclosporin: Reduced blood levels with risk of transplant rejection

Oral Contraceptives: Reduced blood levels with risk of unintended pregnancy

Anticonvulsants: Reduced blood levels with risk of seizures

Digoxin: Reduced blood levels and loss of control of heart rhythm or heart failure

Theophylline: Reduced blood levels and loss of control of asthma

Triptans & SSRIs: Increased serotonergic effects with increased incidence of adverse reactions.

REFERENCES

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2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.