

5.3. ANTIMALARIALS



5.3.1. Introduction

Antimalarials are drugs used effectively in the treatment of malaria. They prevent or relieve the malarial symptoms. Most antimalarial drugs target the erythrocytic stage of malaria infection, which is the phase of infection that causes symptomatic illness.

5.3.2. Cinchona

Cinchona is a tall, evergreen tree which on maturing attains a height of 50-100 feet. The medicinally important part of cinchona tree is the bark from which quinine alkaloid is extracted and used in the treatment of malarial infection.

Synonyms

Jesuit's bark, Peruvian bark, and Calisaya bark.

Biological Source

Cinchona is the dried bark of the stem or root of *Cinchona succirubra*, *C. ledgeriana*, and *C. calisaya*.

Family

Rubiaceae.

5.3.2.1. Occurrence and Distribution

Cultivation of cinchona for commercial purpose is done in Sri Lanka, Indonesia, Bolivia, Columbia, Ecuador, and Kenya. In India, it is cultivated in Annamalai Hills and Nilgiri Hills (in Tamil Nadu), as well as in Darjeeling district of West Bengal.

5.3.2.2. Organoleptic Evaluation

The organoleptic characteristics of cinchona plant are described below:

- 1) **Stem-Bark:** 30cm long and 2-6mm thick; bark for manufacturing purposes is available in small curved pieces; the **outer surface** of the stem bark has moss or lichen; longitudinal and transverse cracks are found on the cork that may vary in frequency and distinctness in different varieties; the cork may or may not be longitudinally wrinkled; the **inner surface** varies from yellowish-brown to deep reddish-brown colour and is striated; fracture is fibrous on the inner side and short on the outer side; stem bark has a very light odour and is bitter or astringent in taste.
- 2) **Root-Bark:** Present in channelled and twisted pieces; usually 2-7cm long; both surfaces have identical colour; outer surface is scaly and the inner surface is striated.
- 3) **Plant:** Description of important species of genus *Cinchona* is given in the **table 5.1**:

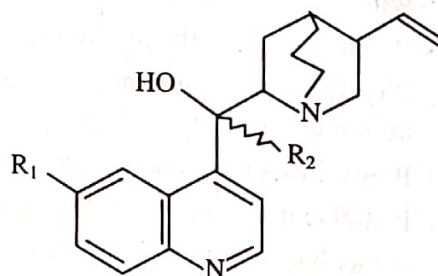
Table 5.1: Comparison of Cinchona Species

<i>C. succirubra</i>	<i>C. calisaya</i>	<i>C. ledgeriana</i>	<i>C. officinalis</i>
20-40mm in diameter and 2-6mm thick.	12-25mm in diameter and 2-5mm thick.	Similar to <i>C. calisaya</i> .	12mm in diameter and 1mm thick.
Well-marked longitudinal wrinkles, relatively few transverse cracks, some pieces show reddish warts.	Broad longitudinal fissures, transverse cracks present about 6-12mm apart.	Similar to <i>C. calisaya</i> , but cracks are more numerous and less deep, some pieces show longitudinal wrinkles and reddish warts.	Numerous transverse cracks present at less than 6mm apart.
Powder reddish-brown.	Powder cinnamon-brown	Powder cinnamon-brown.	Powder yellowish.

5.3.2.3. Chemical Constituents

The amount of alkaloids and their ratios vary in different species and hybrid depending on the environment of tree, age, and collection method of the bark.

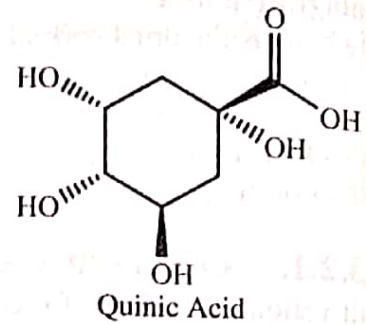
From cinchona bark, quinoline alkaloids are obtained. Most important alkaloids are stereoisomers quinine and quinidine and their respective 6'-demethoxy derivatives, **cinchonidine** and **cinchonine**. Quinine is the most important alkaloid and the other less significant alkaloids are **quinicine** and **cinchonicine**.



Quinine ($R_1 = \text{OCH}_3$, $R_2 = \alpha\text{-H}$)
 Quinidine ($R_1 = \text{OCH}_3$, $R_2 = \beta\text{-H}$)
 Cinchonidine ($R_1 = \text{H}$, $R_2 = \alpha\text{-H}$)
 Cinchonine ($R_1 = \text{H}$, $R_2 = \beta\text{-H}$)

In the parenchymatous tissues of bark, **quinic acid** (5-8%) and **cinchotannic acid** are present in combination. Cinchotannic acid is a phlobatannin and a considerable amount of its decomposition product, 'cinchona red', is found in the bark.

Another constituent is a glycoside, **quinovin** (2%) which on hydrolysis yields quinovic acid and quinovose (isorhodoose).



5.3.2.4. Chemical Tests

The chemical tests for cinchona are:

- 1) **Thalleoquin Test:** On treating the powdered drug with bromine water and dilute ammonia solution, emerald green colour develops.
- 2) On slightly moistening cinchona bark with glacial acetic acid and heating in a test tube, blood-red drops appear on the side of the tube.
- 3) On moistening cinchona bark with sulphuric acid, a blue fluorescence is observed under UV light.
- 4) On treating quinidine solution with silver nitrate solution, a white precipitate is obtained which is soluble in nitric acid.

5.3.2.5. Therapeutic Efficacy

Cinchona and its constituents have the following therapeutic uses:

- 1) Its bark is used as an antimalarial, antipyretic, and analgesic.
- 2) Its bark is also used as an antiseptic in the treatment of abscesses, cavities, ulcers, as a mouthwash and gargle in sore-throat.
- 3) Cinchona is used in the treatment of small pox, septic fevers, pneumonia, acute rheumatism, tonsillitis, nasal catarrh, pyaemia (blood poisoning), etc.
- 4) It is also used in the treatment of whooping cough, hay-fever, spleen enlargement, hemicranias, and other neuralgic infections.
- 5) The barks and all cinchona preparations are valuable in intermittent fever.
- 6) They have been prescribed as tonic in dyspepsia, gastric catarrh, adynamia and convalescence from fever.
- 7) It is a good ingredient in dentifrice.
- 8) Quinine and quinidine have cardio-depressant activity.
- 9) Quinidine shows antiarrhythmic activity.
- 10) It is also used in the prophylaxis of cardiac arrhythmias and atrial fibrillation.
- 11) Phytochemical quinine isolated from cinchona alkaloids is the most potent antimalarial agent.
- 12) It also has antipyretic action.
- 13) It is also used to treat leg cramps caused by vascular spasm.
- 14) It has bacteriostatic properties, and is highly active against *in vitro* protozoans and also prevents yeast fermentation.
- 15) A mixture of quinine and urea hydrochloride is injected as a sclerosing agent in the treatment of internal haemorrhoids, varicose veins, and pleural cavities after thoracoplasty.

5.4. OXYTOCICS

5.4.1. Introduction

Oxytocics are drugs which stimulate the contraction of smooth muscles of uterus. The administration of an oxytocic can initiate and enhance rhythmic uterine contraction at any time, but relatively high doses are required for such responses in early pregnancy. Oxytocic agents commonly used include oxytocin, certain prostaglandins, and the ergot alkaloids.

These drugs are used for induction and augmentation of labor at term, control postpartum haemorrhage, correct postpartum uterine atony, produce uterine contractions after cesarean section or other uterine surgery, and induce therapeutic abortion. These drugs are used with extreme caution in parturients with severe hypotension and hypertension, partial placenta previa, cephalopelvic disproportion, or grand multiparity. The risk of using these agents is much higher in mothers who have undergone recent uterine surgery or who have suffered recent sepsis or trauma. The most serious adverse reaction is sustained tetanic contraction of the uterus, resulting in foetal hypoxia or rupture of the uterus.

5.4.2. Ergot

Ergot of Rye is a fungal disease of wheat and rye caused by a fungus *Claviceps purpurea*. Grain of rye and wheat are replaced by a dark, purplish **sclerotium**. After winter, the sexual-phase of the lifecycle of ergot starts from **sclerotium**.

Synonyms

Ergot of Rye and Ergota.

Biological Source

Ergot is the dried sclerotium of a fungus, *Claviceps purpurea* Tulasne, found in the ovary of the rye or *Secale cereal*.

Family

Clavicipitaceae

5.4.2.1. Occurrence and Distribution

Ergot is produced by controlled field cultivation of fungus on rye and is commercially produced in Czechoslovakia, Hungary, Switzerland, and former Yugoslavia.

5.4.2.2. Organoleptic Evaluation

Ergot consists of sclerotium (plural sclerotia) having the following characteristic features (figure 2.17):

- 1) **Shape:** Fusiform and slightly curved; transverse section of sclerotia is triangular or four-sided.
- 2) **Size:** 1-4cm long and 2-7mm broad.
- 3) **Colour:** Outer surface is dark, violet-black coloured.
- 4) **Odour:** Characteristic (disagreeable and fainting type).
- 5) **Taste:** Unpleasant.
- 6) **Other Features:** Fractured pieces exhibit thin, dark outer layer, a whitish or pinkish-white central zone of pseudoparenchyma having darker lines radiating from centre.

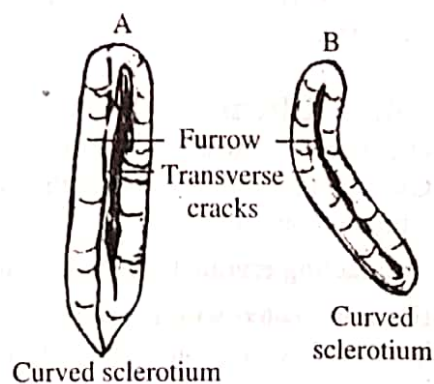


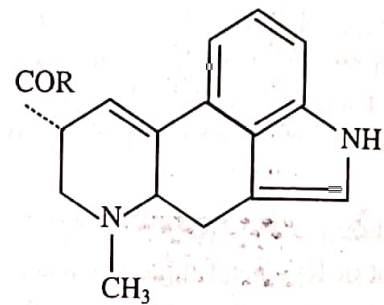
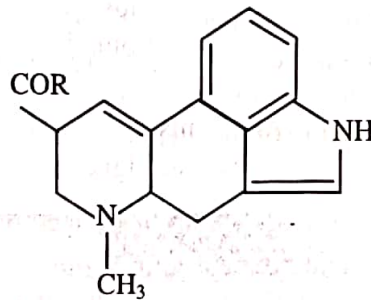
Figure 5.3: T.S. of Sclerotium

5.4.2.3. Chemical Constituents

Chemically, ergot alkaloids are **indole alkaloids** that are peptide derivatives of lysergic acid. Therefore, these alkaloids are also known as **peptide alkaloids**, and its concentration is around 0.1-0.25%.

Table 5.2: Ergot Alkaloids

Type	Group	Lysergic Acid	Isolysergic Acid
Water-Soluble (Amino Alcohol)	Ergometrine	Ergometrine (ergonovine)	Ergometrinine
Water-Insoluble (Polypeptides)	Ergotamine	Ergotamine, ergosine	Ergotaminine, ergosinine
	Ergotoxine	Ergocristine	Ergocristinin
		Ergocryptine, ergocornine	Ergocryptinine, ergocorninine



R = -OH

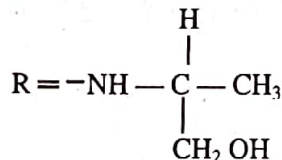
Lysergic acid

Isolysergic acid

R = -NH₂

Lysergic acid amide
(Ergine)

Isolysergic acid amide
(Erginine)



Ergometrine

Ergometrinine

R = -N(C₂H₅)₂

Lysergic acid diethylamide (LSD)

Clavin-type alkaloids, histamine, amino acids, colouring matter (sclererythrin), ergosterol, fungisterol, chitin (cell-wall component of hyphae) are the other constituents of ergot. **LSD** (Lysergic Acid Diethylamide) is a semi-synthetic compound of ergot used in psychiatry.

5.4.2.4. Chemical Tests

The chemical tests which ergot gives are:

- 1) On treating ergot powder with Van-Urk's reagent (*p*-dimethyl amino benzaldehyde), a blue colour develops.
- 2) On reacting ergometrine with water, a blue fluorescence is observed.
- 3) Ergot is treated with ether and sulphuric acid. After filtering the solution, the filtrate is treated with a saturated solution of sodium bicarbonate resulting in a red-violet coloured aqueous layer.
- 4) A small quantity of ergotamine is dissolved in glacial acetic acid and ethyl acetate solution. Small quantity of this solution is shaken with sulphuric acid resulting in a blue colour with a red tinge. On adding ferric chloride, the red tinge fades away, while the blue colour deepens.

5.4.2.5. Therapeutic Efficacy

Ergot and alkaloids extracted from it have the following therapeutic uses:

- 1) Ergotamine tartrate is used as an analgesic for treating migraine.
- 2) Ergotoxine methanesulphonates (mesylates) are used in geriatric patients for migraine.
- 3) Ergot and ergometrine maleate are used as oxytocic to enhance labour pain during delivery and also to prevent post-partum haemorrhage.
- 4) Lysergic Acid Diethylamide has a psychotomimetic action, therefore, is used in the treatment of psychiatric patients.
- 5) It is used for treatment and prophylaxis of post-abortion or postpartum bleeding.
- 6) It is used for treating menorrhagia, menopausal bleeding, and uterine atony.
- 7) Bromocriptine pergolide derivative is used to treat hyper-prolactinaemic infertility and prolactin-secreting pituitary tumours.
- 8) Ergoloid mesylates (dihydrogenated ergot alkaloids, e.g., dihydroergocornine, dihydroergocristine and dihydroergocryptine in combination) are used for relief of symptoms of senility.
- 9) Bromocriptine is used to treat Parkinsonism, suppression of lactation, hypogonadism, acromegaly, galactorrhoea, and mastalgia. (12)