# Pharmacognosy and Phytochemistry

## Alkaloids-Part 6

**B. Pharm. Semester-1**

**Course Code: 0510221; Session: 2022-2023**

**Dr. BALAKUMAR CHANDRASEKARAN**

**Professor-Faculty of Pharmacy**

**Philadelphia University-Jordan**

# Learning Outcomes

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

**Isoquinoline group of alkaloids**:-

Opium alkaloids

Emetine and cephaeline

Berberine

Curare alkaloids (Bis-benzylisoquinoline type)

Amaryllidaceae Alkaloids (Galanthamine; Tyrosine-derived alkaloid)

# Objective

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

# Isoquinoline alkaloids

1. **Opium alkaloids**

   **A. Modefied benzyl-tetrahydro-isoquinoline alkaloids (Papaverine, Noscapine)**

   **B. Morphinan alkaloids** or **Phenanthrene derivatives (Morphine, Codeine and Thebaine)**

2. **Tetrahydro-isoquinolin or Benzophenanthridine alkaloids (Berberine and Sanguinarine)**
3. **Terpenoid Tetrahydroisoquinoline** Alkaloids

   **(Emetine, Cephaline and Psychotrine)**
4. **Curare alkaloids (Bis-benzylisoquinoline)**
5. **Amaryllidaceae Alkaloids (Galanthamine)** (Tyrosine-derived alkaloid)

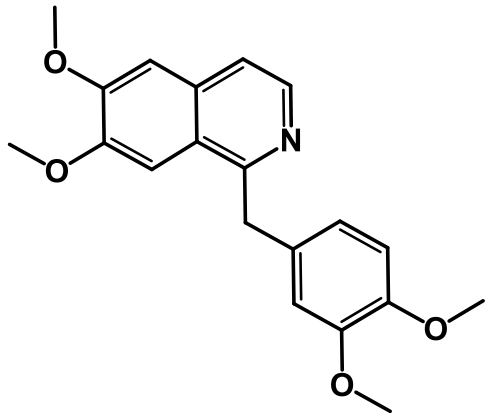
# Opium alkaloids

- Opium is dried latex (milky exudates) obtained from the seed/unripe capsules of the opium poppy, *Papaver somniferum*.
- Approximately 12% of opium is made up of analgesic alkaloid **morphine**, which is processed chemically to produce heroin and other synthetic opioids for medicinal use.
- The latex also contains the closely related opiates: **codeine** (2.5-5%), and **thebaine** (less than 1%), and non-analgesic alkaloids such as **papaverine** and **noscapine**.


Opium Poppies in Northern Thailand
photo by John W. Allen

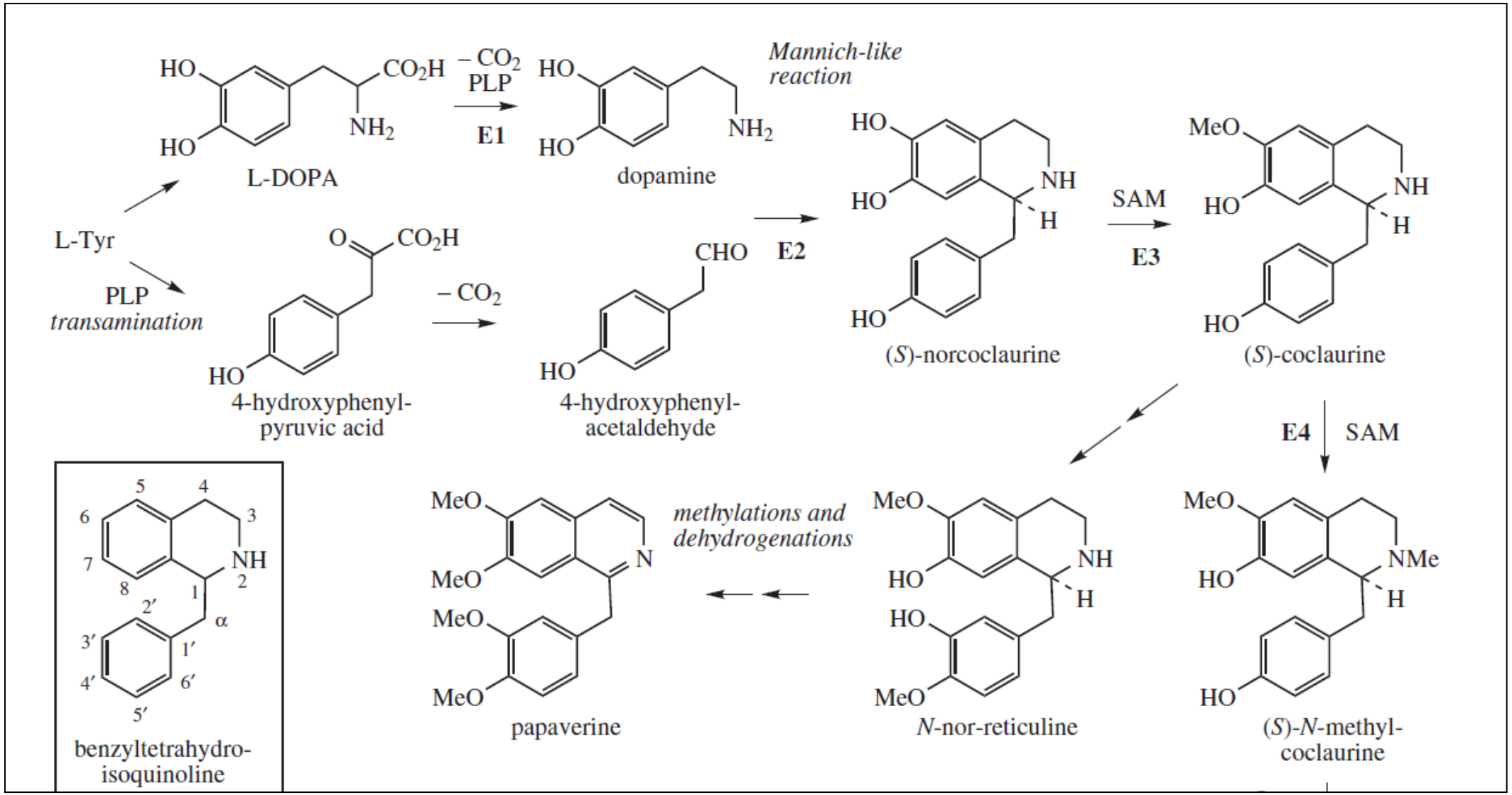
# Opium alkaloids: Benzyl isoquinoline type: Papaverine

- An opium alkaloid isolated from the plant *Papaver somniferum* , الخشخاش المنوم and is also produced synthetically.
- Effect: a direct-acting **smooth muscle relaxant**.
- Papaverine: Used to increase blood flow throughout the body, including the heart and the brain.
- Papaverine is a **vasodilator** by relaxing the muscles in the blood vessels.
- Papaverine is also an **antiarrhythmic** medication that treats certain abnormal heartbeats (ventricular arrhythmias).




Papaverine

# Opium alkaloids: Papaverine: Biosynthesis

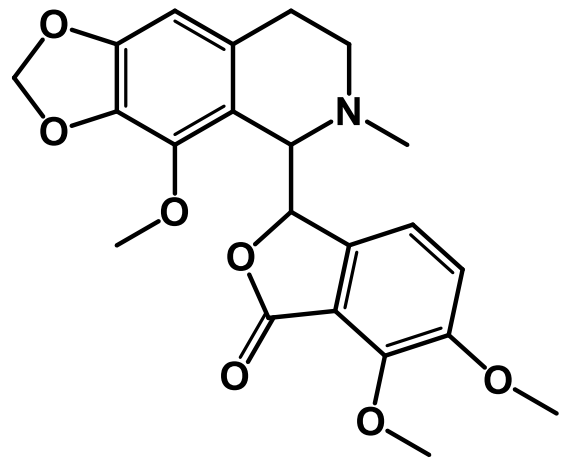


# Opium alkaloids: Papaverine: Pharmacological actions

1. Papaverine decreases the tone of smooth muscles, thus, It has a spasmolytic and vasodilating effect {used to increase blood flow}.
2. It is neither narcotic nor addictive.
3. It is having a beneficial effect on angina pectoris.
4. It is used for treatment of pulmonary embolism and cerebrovascular thrombosis.
5. It is also used as an Anti-arrhythmic.

# Opium alkaloids:
# Benzyl-tetrahydroisoquinoline type: Noscapine

- An opium alkaloid (4-5%) isolated from the plant *Papaver somniferum*
- Effect: a **direct-acting smooth muscle relaxant**.
- **Noscapine**: It is used as antitussive with no analgesia or sedation or narcotic or hypnotic activity.




**Noscapine**

# Opium alkaloids: Isoquinoline type: Morphine

- An opium alkaloid isolated from the plant *Papaver somniferum*
- Morphine is a powerful analgesic and narcotic, however with a number of serious side effects are possible (both in CNS and peripherally).
- It binds stereo-specifically and reversibly with high affinity to μ-opioid receptor.

**CNS activity**:-

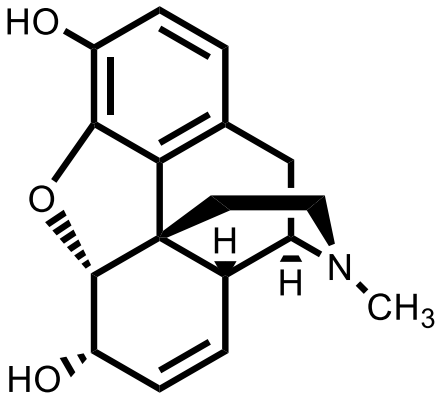
1. **Analgesic effect**: reduces pain perception, induces indifference toward pain.
2. **Respiratory effects**: Morphine depresses the respiratory centers in the brain. At higher dose bradypnea and irregular breathing rhythm appear.
3. **Antitussive effect**: Morphine depresses the cough center.

# Opium alkaloids: Isoquinoline type: Morphine

**Peripheral activity**:-

1. **Digestive effects:** Nausea and vomiting (not in all patients). Decreases peristalsis and may result in long lasting constipation.
2. **Urinary retention:** anti-diuretic effect.
3. **Peripheral vasodilation:** May result in hypotension.
4. **Bradycardia**
5. **Shortening of breath**

**Morphine**




# Opium alkaloids: Isoquinoline type: Morphine

**Medicinal Uses of Morphine**:-

- ✓ **Analgesic** (Pain killer) in severe traumas, cancer and myocardial infarction.
- ✓ Major part of morphine is converted to various other compounds such as codeine, ethylmorphine, pholcodine, oxycodone, nalorphine, and naloxone.
- ✓ The worldwide demand for opiates for medicinal applications is equivalent to approx. 190 metric tons of morphine, with about 80% of the global needs for codeine.

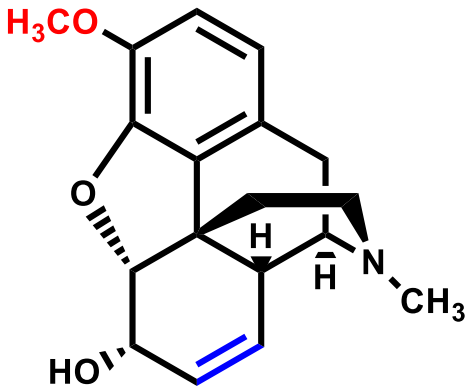
**Side effects of Morphine**:-

Morphine develops psychological and **physiological dependence**, followed by tolerance (need for larger and frequent doses).

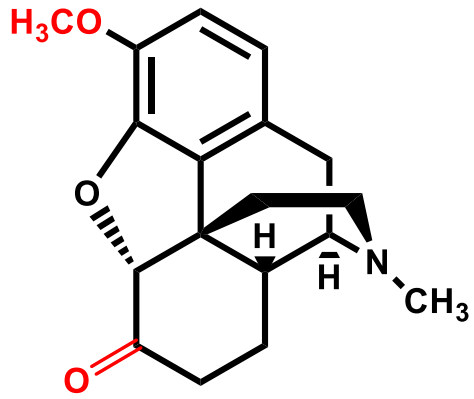
The discontinuation of morphine administration in chronic user causes a withdrawal symptoms, such as rhinorrhea, sweating, lacrimation, agitation , mydriasis, pain in the joints and in the muscles, anxiety, insomnia, tachycardia, nausea and diarrhea.

# Opium alkaloids: Isoquinoline type: Codeine

1. **Antitussive activity**
2. **Analgesic:** acting like morphine, but less active narcotic, used to treat mild to moderate pain. Codeine and its derivative hydrocodone in combination with paracetamol are indicated for the symptomatic treatment of pain. Codeine is less toxic and much weaker in action than morphine with less development of tolerance.
3. **Anti-diarrheal** agent.



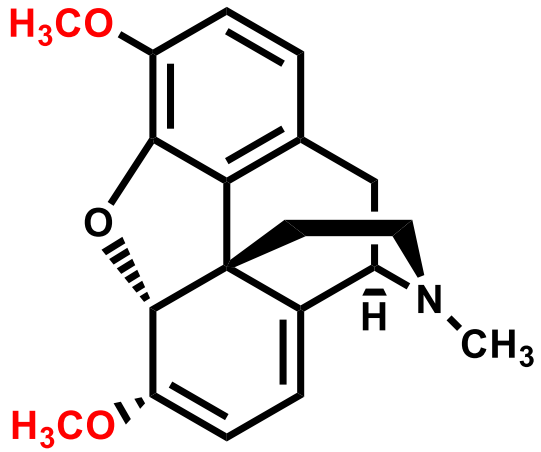

**Codeine**




**Hydrocodone**

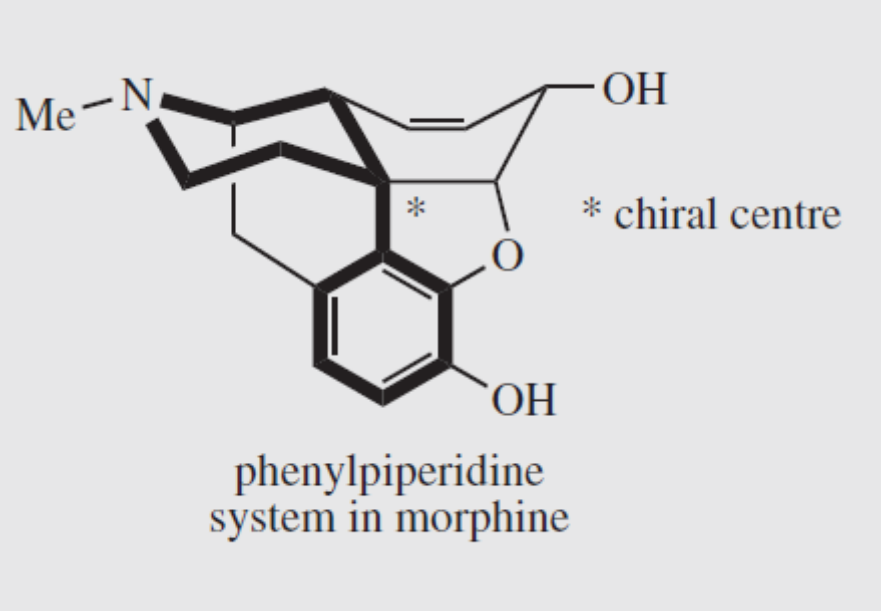
# Opium alkaloids: Isoquinoline type: Thebaine

1. **No analgesic activity**, but used as morphine antagonist.
2. It is converted industrially into a variety of compounds including oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine.




**Thebaine**

# Basic structural requirements for analgesic activity

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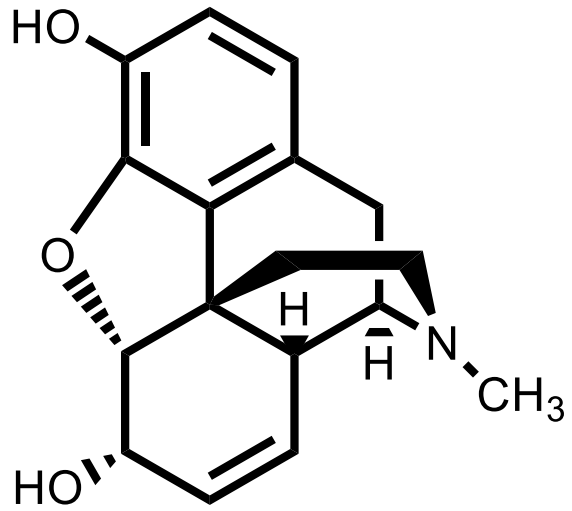
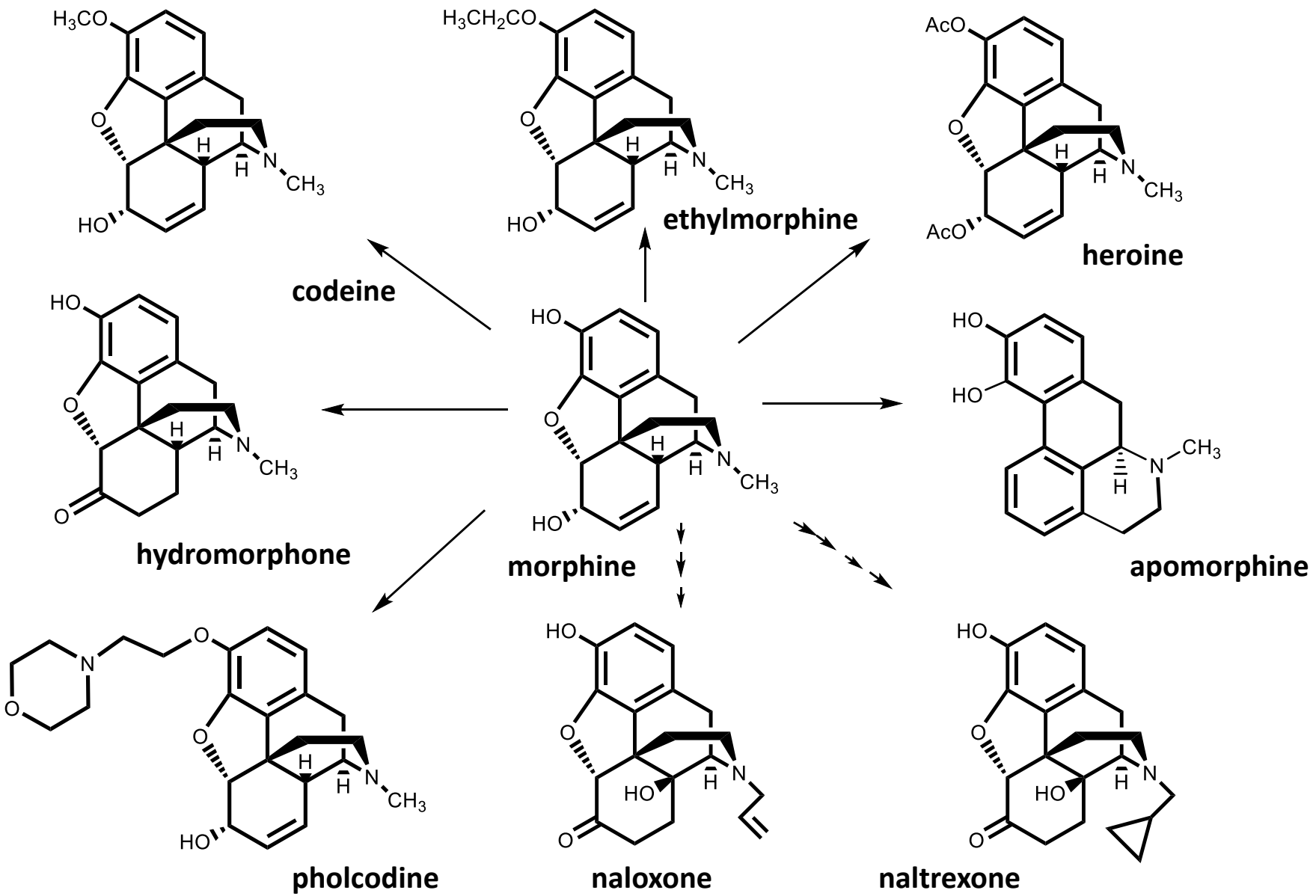



It has been found that a common structural feature required for centrally acting analgesic activity in the opioids is the combination of aromatic ring and a piperidine ring which maintain the stereochemistry at the chiral center.

# Semisynthetic derivatives of Morphinane

- **Hydromorphone** obtained from morphine has strong analgesic activity and is used for **severe pain associated with cancer.**
- **Pholcodine** is an effective antitussive
- **Ethylmorphine** used as **antussive for dry cough**. It is also a strong analgesic
- **Heroine** is a highly addictive analgesic and hypnotic.
- **Apomorphine** has no analgesic properties, is a **powerful emetic** used for emergency treatment of poisoning and to control the symptoms of Parkinson's disease.
- **Nalorphine**: **partial agonist** to Morphine, interrupts the effect of morphine by displacing it from the receptors to where it binds.
- **Naloxone** is a **potent antagonist** at all opioid receptors and is used to treat opiate poisoning.
- **Naltrexone** has **antagonistic activity** at all opioid receptors, similar to naloxone

# Semisynthetic Morphinane Alkaloids

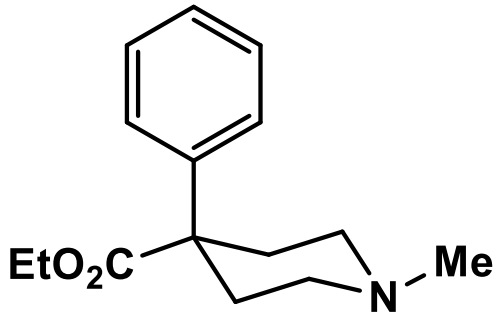


# Synthetic derivatives of Morphinane

- **Pethidine** (meperidine) less potent than morphine, but produces prompt, **short-acting analgesia** and is also less constipating than morphine.
  It can be addictive, so not used for chronic pain.
- **Fentanyl** is 50-100 times **more active than morphine**. It has high lipophilicity, excellent transport properties and administered transdermally.
- **Methadone** is orally active, having similar activity to morphine, but is **less euphorigenic** and has longer duration of action. Potentially addictive, but withdrawal symptoms are milder, so it is used to treat heroin drug addicts.
- **Tramadol**: A new **analgesic** drug. It acts by two mechanisms: morphine mechanism and serotonin-adrenergic pathway. It produces morphine-like side effects.
- **Etorphine**: It is 5000 -10,000 times **more potent than morphine**.
  It is used as an **analgesic** for large animals like elephants.

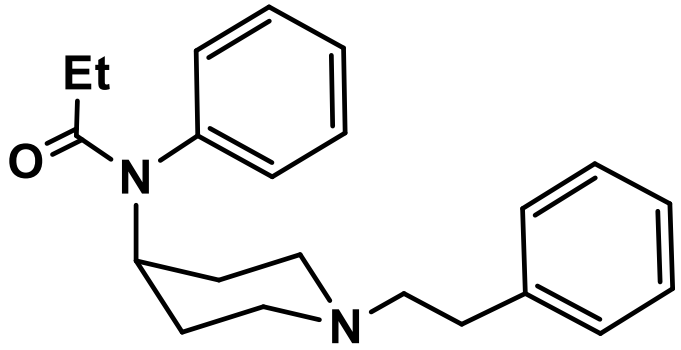
# Synthetic derivatives: Structures and Formulations

## Pethidine



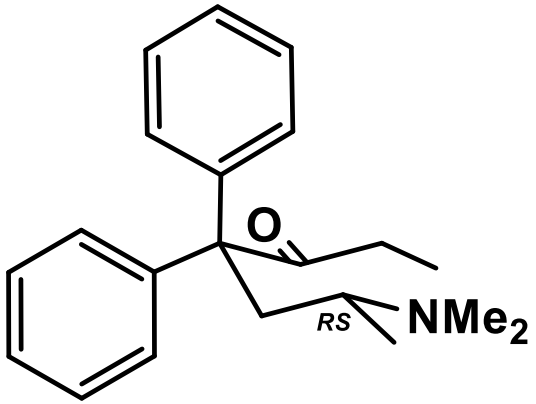


## Fentanyl

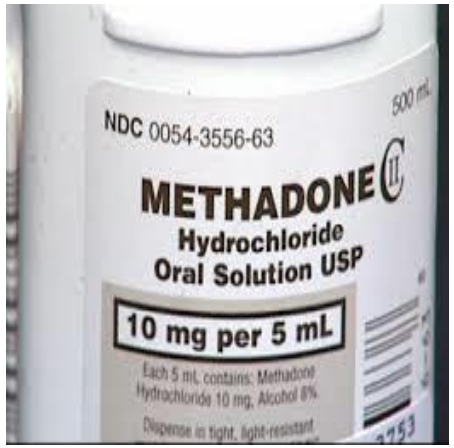



Fentanyl

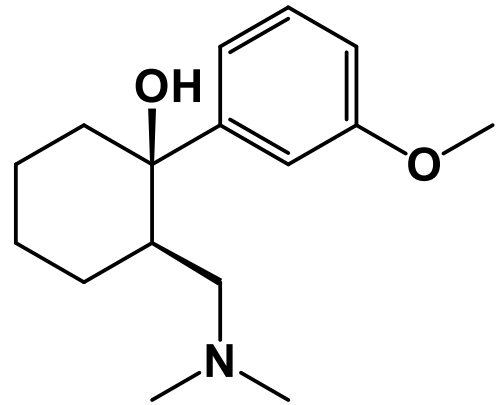

## Methadone




Methadone

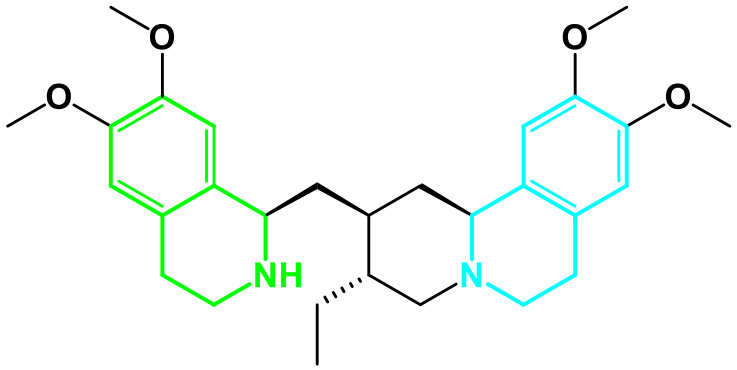



## Tramadol

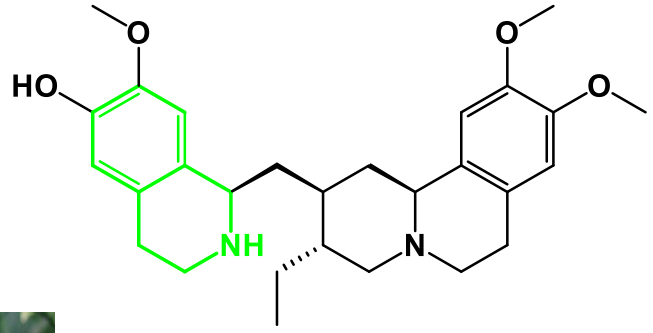



# Ipecac alkaloids: 2-benzyltetrahydroisoquinoline type

- 2-Benzyltetrahydroisoquinoline type of Ipecac alkaloids are **Emetine**, **cephaeline**, and **psychotrine**.
- These alkaloids are obtained from the roots of *Cephaelis ipecacuanha*, family: Rubiaceae, a shrubby small plant native to tropical forest of Brazil .




Emetine




Cephaeline

# Ipecac alkaloids: Emetine and Cephaline

- **Emetine**: **anti-protozoal** and to induce vomiting (**Emetic**) and **expectorant**.
- **Cephaeline**: to induce vomiting (**emesis**).
- They irritate mucous membranes of stomach and intestine locally and produce emesis.

**Pharmacological actions of Emetine and Cephaline**:

1. For **dysentery** (Entamoeba histolytica): by inhibiting protein synthesis in the protozoal cell by binding to 40s ribosomal subunit and inhibiting at the translocation stage.
2. For poisoning cases in hospitals.
3. In small doses, emetine and cephaline are **expectorants**.
4. It has anticancer effect, but its effect is marginal and toxic to heart.

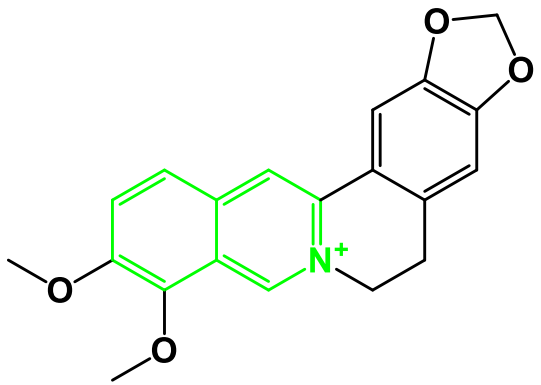
**O-methylpsychotrine**: It has displayed fairly low effects on protein synthesis, but quite potent ability to curb viral replication through inhibition of HIV reverse transcriptase, used for the **treatment of AIDS**.

# Benzylisoquinoline alkaloids: Berberine

**Berberine:** It is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in Berberis vulgaris, Family: Berberidaceae.

**Berberine** is used as an **antiemetic**, **antibacterial** and **anti-inflammatory**.

It is also used for the treatment of liver diseases and diabetes.

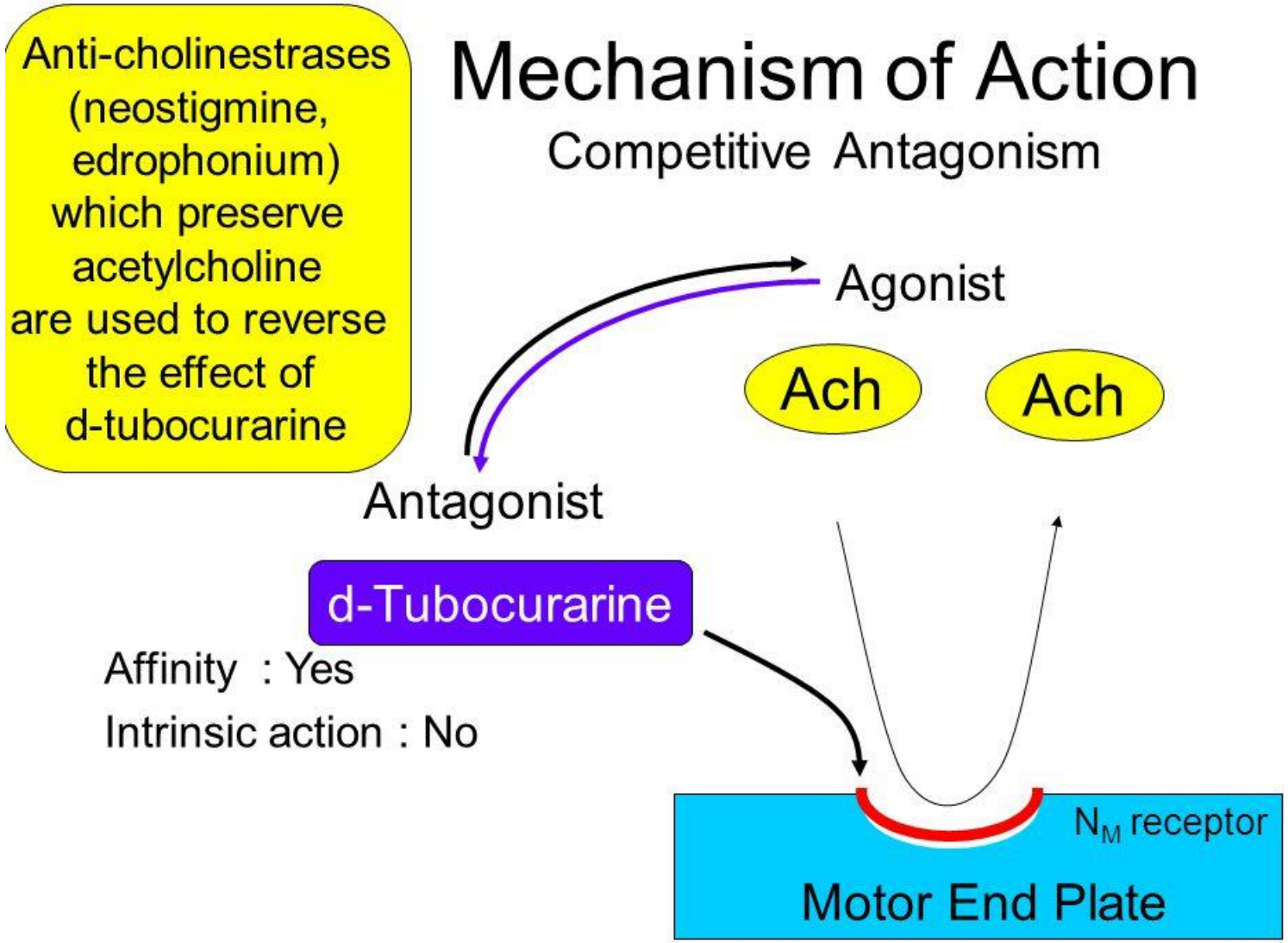



Berberine

# Curare alkaloids: d-Tubocurarine (DTC)

- ✓ **Curare alkaloids**: *d*-Tubocurarine (DTC) belongs to Bis-benzylisoquinoline type of structure.
- ✓ It is obtained from the bark and stems of *Chondrodendrum tomentosum* family: Menispermaceae.
- ✓ The term “curare” is used to indicate the crude extract prepared from different species.
- ✓ It was used by certain natives of the Amazon regions of South America as **arrow poison**.
- ✓ Some of these extracts were poisonous by virtue of a convulsant action and others by **paralyzing action** on voluntary muscles (Most remarkable).
- ✓ It has toxic effect on blood vessels and show histamine–like effect.
- ✓ Most of the activity is attributed to ***d*-tubocurarine** (DTC).

# Mechanism of action of *d*-Tubocurarine (DTC)



# Uses of Curare Alkaloids

## Uses of Curare Alkaloids:-

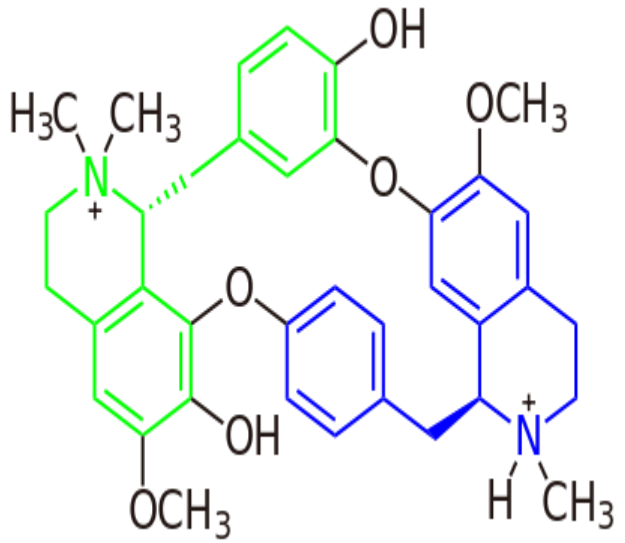
1- In **surgical anesthesia**, as it produces muscular relaxation without deep anesthesi

2- After shock treatment (in mental diseases) as it **reduces convulsions**.

3-To **control convulsions** after strychnine poisoning

(Strychnine increases excitability)

***d*-Tubocurarine (DTC)**



# Amaryllidaceae Alkaloids: Galanthamine

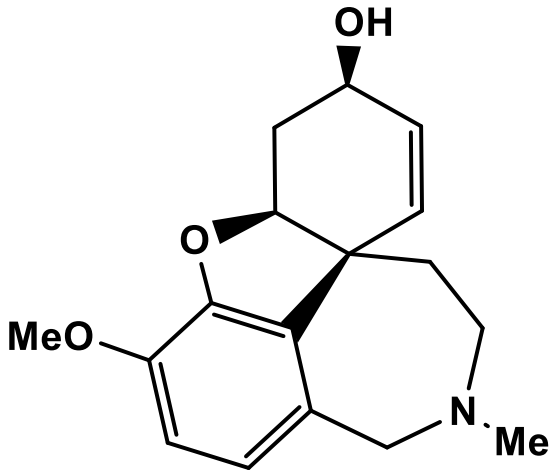
**Galantamine**: It is used for the treatment of cognitive decline in mild to moderate **Alzheimer's disease** and various other memory impairments.

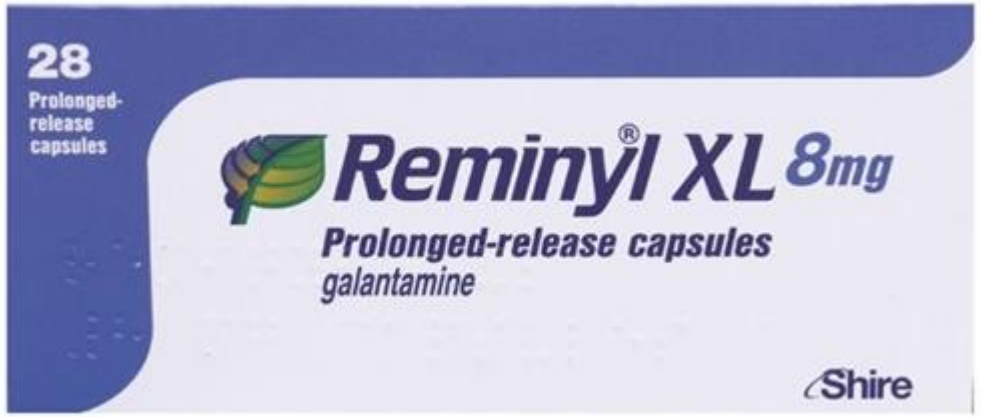
- It is an alkaloid that has been isolated from the bulbs and flowers of *Galanthus nivalis* (Common snowdrop), Family: Amaryllidaceae.
- Galanthamine is selective **acetylcholinesterase inhibitor**.
- It acts in CNS by penetrating blood-brain barrier
- Galanthamine (Reminyl®) was approved for symptomatic treatment of the early stage of **Alzheimer disease**.

# Amaryllidaceae Alkaloids: Galanthamine

**Snowdrops**
**(*Gallanthus* spp)**

**Galanthamine**



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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.**