Approximately alkaloid obtained from the roots of *Vinca rosea* (*Catharanthus roseus*) and the roots of *Rauwolfia serpentina*.

**Uses:**
1. Antihypertensive.
2. To increase the blood flow in the brain and in the peripheral parts of the body.

*Rauwolfia Alkaloids:*

**Botanical source:** root of *Rauwolfia serpentina* (*Apocynaceae*).
**Examples:** reserpine and rescinnamine.
**Reserpine was an important antihypertensive drug.**
**It also has a tranquilizing effect.**
**High doses could cause mental fatigue and depression.**

**Mechanism of action:** anti-hypertensive; depletion of catecholamines peripherally (decrease in epinephrine and norepinephrine), depletion of central neurotransmitter (mainly serotonin and norepinephrine). **Unstable compound due to existence of an ester linkage.**
Isoquinoline Alkaloids
Isoquinoline alkaloids

- This group include the followings:
  1. **Benzyl isoquinoline type:**

**Papaverine:**
- An opiate alkaloid isolated from the plant *Papaver somniferum* and is also produced synthetically.
- **Effect:** a direct-acting smooth muscle relaxant.

Morphinan type alkaloids:

**Morphinan:** the prototype structure of numerous drugs including opiate analgesics, cough suppressants...etc.

**Opium alkaloids:**

- **Botanical source:**
  - Dried latex of *Papaver somniferum* - *Papaveraceae*
Pharmacology:
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 of a beneficial effect on **angina pectoris**.
4. It is used for treatment of **pulmonary embolism** and **cerebrovascular thrombosis**.
5. Anti-arrhythmic.

Pharmacological action and medicinal uses:

**Morphine:**
1. potent analgesic and pain-killer in several cases and ailments such as: myocardial infarction, cancer, renal colic, bone and joint pain ..etc.
2. Cough supressant and anti-diarrheal (severe). However they are other more convenient drugs for these two cases.

**Codeine:**
1. Analgesic to treat mild to moderate pain.
2. Anti-tussive.
3. Anti-diarrheal.

**Thebaine (codeine methyl enol ether):**
- Thebaine is not used for therapeutic or recreational purposes, but is converted industrially into a variety of compounds including oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine.
Papaverine:
1. Used to increase blood flow throughout the body, including the heart and the brain. Papaverine is a vasodilator. It works by relaxing the muscles in the blood vessels.
2. Papaverine is also an antiarrhythmic medication that treats certain abnormal heartbeats (ventricular arrhythmias).

Heroin:
1. Strong analgesic and pain-killer, like morphine, to relieve severe pain (e.g. myocardial infarction, injuries ...etc)
2. As a maintenance drug among heroin addicts.
3. As a substitute for morphine as a pain-killer as it is more lipid-soluble.

Noscapine: is devoid of pain-killing properties.
• Anti-tussive.

• Noscapine (previously narcotine):
  Ø It is a benzylisoquinoline (like papaverine).
  Ø Found in Papaver somniferum (opium) 4-8%.

Pharmacology:
• Smooth muscle relaxant effect.
• It is used as antitussive with no analgesia or sedation.
• It is devoid of any narcotic or hypnotic activity.
• **Noscapine** (previously narcotine):
  - It is a benzylisoquinoline (like papaverine).
  - Found in *Papaver somniferum* (opium) 4-8%.

**Pharmacology:**
- Smooth muscle relaxant effect.
- It is used as antitussive with no analgesia or sedation.
- It is devoid of any narcotic or hypnotic activity.

2. **Benzyltetrahydroisoquinoline: Ipecacuahna alkaloids:**
- Rhizome of *Cephaelis ipecacuana* (*Rubiaceae*)
  - **Emetine:** anti-protozoal and to induce vomiting.
  - **Cephaeline:** to induce vomiting (emesis).
2. Benzyltetrahydroisoquinoline:

Ipecacuahna alkaloids:
- Rhizome of *Cephaleis ipecacuhana* (*Rubiaceae*)
- **Emetine**: anti-protozoal and to induce vomiting.
- **Cephaeline**: to induce vomiting (emesis).

**Goldenseal**:
Root and rhizome of *Hydrastis canadensis* (*Ranunculaceae*).

**Catarrha**: inflammation of a mucous membrane, especially of the respiratory tract, accompanied by excessive secretions.

**Uses**: anti-catarrhal, anti-inflammatory, antispetic, astringent, bitter tonic (stimulate appetite), anti-diabetic.
Hydrastine

- Found in the roots and rhizomes of *Hydrastis canadensis* (family: *Ranunculaceae*).

**Uses:**
- To control uterine hemorrhage.
- Traditional use of this root as:
  1. **Tonic** (a medicine that strengthens).
  2. Uterine hemorrhage.
  3. Catarrhal conditions.

Berberine:
- From Berberidaceae (Berberies species) and Ranunculaceae (Hydrastis).
- Used as antiemetic, antibacterial and anti-inflammatory.
- Also, it is used for liver diseases.

Sanguinarine:
- From the roots of *Sanguinaria canadensis* (blood root) (Family *Papaveraceae*).
- Native to America.
- Its effect resembles colchicine, i.e. causes doubling of chromosomes number (polyploidy).
- Used for atonic dyspepsia with hepatic symptoms.
Benefits:
Antifungal, antibacterial, antidiabetic antiinflammatory.

Jatrorrhizine
A protoberberine alkaloid

Berberine
A quaternary amine alkaloid.

Curare alkaloids:

- **Bis-benzylisoquinoline.**
- Obtained from the bark and stems of *Chondrodendrum tomentosum* (family: *Menispermaceae*).

- The name is derived from “urari”; an Indian word indicating “poison”.

- The term “curare” is used to indicate the crude extract prepared from different species.

- 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 (Most remarkable).
Curare possesses:
1. A paralyzing effect on voluntary muscles.
2. A toxic effect on blood vessels.
3. A histamine-like effect.
   - Most of the activity is attributed to α-tubocurarine.

Uses:
1. In surgical anesthesia, as it produces muscular relaxation without deep anesthesia.
2. After shock treatment (in mental diseases) as it reduces convulsions.
3. To control convulsions after strychnine poisoning (Strychnine increases excitability)

Toxiferine is a curare toxin.
It is a bisindole alkaloid derived from Strychnos toxifera and a nicotinic acetylcholine receptor antagonist.
**Toxiferine**:
- Is a curare toxin.
- It is a *bisindole* alkaloid derived from *Strychnos toxifera*.
- It is a *nicotinic acetylcholine receptor antagonist*.
- Therefore, it is a muscle relaxant that causes the paralysis of the skeletal muscles.

**Opium Alkaloids**

- OPIUM is the air-dried milky exudates (latex) obtained after the incision of the unripe capsules of *Papaver somniferum*, {family: *Papaveraceae*}.
- The word *opium* comes from a Greek word which means "poppy juice".
- The name "morphine" was derived from a Greek word "Morpheus": the god of dreams.
- Opium is reported to contain many alkaloids (about 40), the most important of them are:
  - Morphine, codeine, thebaine, papaverine, noscapine and narceine.
They are divided into 4 groups according to structures:
2. Phenylethylamine: e.g., narceine.
3. Diisoquinoline: e.g., cryptopine.
4. Phenanthrene: e.g., morphine, codeine, thebaine.

• Phenanthrene alkaloids:

These are important alkaloids in opium, morphine (8-10%), codeine (0.5-2%) and thebaine (0.1-1%).
Pharmacology:

- The pharmacological action of opium is mainly due to morphine.
- It acts first as a stimulant, then as a sedative and hypnotic depressing the CNS.

**Effect:**
1. Analgesia.
2. Miosis (differentiate from *meiosis*).
3. Euphoria.
4. Respiratory depression.
5. Sedation.
6. Physical dependence.
7. Bradycardia.
8. Constipation.
**Adverse effects:**

1. Constipation.
2. Sedation.
3. Nausea and vomiting.
4. Respiratory depression.
5. Hypersensitivity.
6. Anticholinergic effect: **dry mouth,** **urinary retention.**
7. CNS excitation.
8. Tolerance: **an increase in dose is required to maintain analgesia.**
9. Dependence: **addiction, if used for a long time.**

**Withdrawal symptoms:**

1. Anxiety.
2. Irritability.
3. Insomnia.
4. Chills.
5. Salivation.
6. Diaphoresis.
7. Nausea.
8. Vomiting.
9. GI cramping and diarrhea.

**Uses:**

**Morphine:**

1. Post-operative analgesic for major operations.
2. Cancer pain (terminal pain).

**Codeine:**

- Mainly used as **antitussive,** it suppresses the coughing center in brain.
- Codeine is less toxic and much weaker in action than morphine with less development of tolerance.
Mechanism of action

Before opioid receptor activation

Ca²⁺ channels \textit{open}

\(\mu, \kappa, \delta\)

K⁺ channels \textit{closed}

Presynaptic neuron

G-protein coupled receptor
Mechanism of Action

All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

They are also involved in:
- Postsynaptic hyperpolarization (increasing $K^+$ efflux)
- Reducing presynaptic $Ca^{++}$ influx

thus inhibits neuronal activity.
Opium is the dried milky exudates, or latex, obtained by incising the unripe capsules of opium poppy.

The plant is an annual herb with large solitary (sole, alone) flowers, either white or pink in color.

The latex is obtained by incision of the ripening capsule (that is changing in color from blue-green to yellow).

The incision is made at night.

The milky exudates ooze out (filtrate out), and they rapidly turn brown and coagulate.

They are collected the next morning by scraping (scratching) from the capsule.

The raw opium is molded into balls or blocks (lumps) and wrapped in poppy leaves and shade-dried.

• The plant is cultivated for Black Market in the following countries:

1. Asia Minor (Turkey).
4. Laos (Near Thailand).
5. Latin America (Mexico and Columbia).

• Official drug is cultivated in:

1. India.
2. China.
1. **Heroin:**
   - It is morphine diacetate.
   - Highly addictive analgesic, with more lipophilicity.
   - More abused drug.

2. **Apomorphine:**
   - Injection of the drug is used for its emetic properties to treat intoxication when vomiting is not contraindicated (as in case of poisoning by caustic alkali, or when the patient is in coma).
   - Vomiting is induced by injecting 10 mg of alkaloid subcutaneously.
   - The alkaloid is also available as sublingual tablets which are used sometimes in recovery of alcoholism.
   - Nowadays, it is less frequently used for this purpose, but is used to control the symptoms of Parkinson’s disease, as it is a stimulator to dopamine receptors.

3. **Nalorphine:**
   - It is an opioid antagonist and partial agonist.
   - It interrupts the effect of morphine by displacing it from the receptors to where it binds.
- It is used to treat the **respiratory insufficiency** due to opiates.
- It is **contraindicated** in drug-addicted patients with risk of withdrawal syndrome.

**Totally synthetic drugs related to morphine:**

1. **Naloxone:**
   - It is an antagonist to morphine.
   - Is used to treat **opiate poisoning including children born to opiate addicts.**

2. **Dextromethorphan:**
   - **Antitussive** effect like codeine with **no analgesic and narcotic effect.**
3. Pethidine [generic name: meperidine]:

- It is less potent than morphine, with a shorter duration of action.
- It is used by addicted people.

4. Fentanyl:

- It is 50-100 times more potent as analgesic than morphine.

5. Methadone:

- Has a similar activity to morphine with longer duration of action and different withdrawal symptoms.
- Is used in rehabilitation program for addict patients.
6. Tramadol:
- A new analgesic drug.
- It acts by 2 mechanisms: morphine mechanism and serotonin-adrenergic pathway.
- It produces typical morphine side effects.

7. Etorphine:
- It is 5000 -10,000 times more potent than morphine.
- It is used as an analgesic in large animals like elephants.
Purine Base Alkaloids:

- The most important alkaloids in this group are the alkaloids derived from the xanthine nucleus (oxidized purine), and these are:
  1. Caffeine.
  2. Theobromine.
  3. Theophylline.

Botanical source:

1. *Cola nitida* (from coat of seeds).
2. *Thea sinensis* or *Camellia sinensis* (from leaves).
3. *Coffea arabica* (from seeds).
5. *Theobroma cacao* (from seeds).
Theobroma cacao

Caffeine

Theophylline

Caffeine
**PHARMACOLOGY:**

1. CNS stimulant.
2. Smooth Muscle relaxant.

For cardiac edema and angina pectoris (because of the diuretic and vasodilating effects, especially for theobromine).

**Proto Alkaloids:**

**Terpenoid alkaloids:**

- Aconitine (20 carbons)
- Atisine (18 carbons)
- Viatichine

**Theobromine**
**Terpenoids**

Any of a large class of organic compounds including terpenes, diterpenes, and sesquiterpenes. They have unsaturated molecules composed of linked isoprene units, generally having the formula \((C_5H_8)_n\).

**Terpenes – classification:**

- monoterpenes \((C_{10})\) 2 x isoprene
- sesquiterpenes \((C_{15})\) 3 x isoprene
- diterpenes \((C_{20})\) 4 x isoprene
- triterpenes \((C_{30})\) 6 x isoprene
- tetraterpenes \((C_{40})\) 8 x isoprene

- formed by bonding „head to tail“ or „tail to tail“
- different degree of unsaturation
- variety of functional groups

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- **Aconite root:**
  - The alkaloids (1. **20 carbon atoms**) of this group is found mainly in species of *Aconitum* and *Delphinium* \(\text{العناق} \text{البيش} \text{(Ranunculaceae)}\).
  - The alkaloids are *aconiine* and *aconitine* from the tuber of *Aconitum napellus*.
  - **Aconite is known to be the most poisonous plant**, 10 gms can kill an adult.
The drug was used in the treatment:

1. Neuralgia [(a stabbing, burning, and often quite severe pain that occurs along a damaged nerve)]
2. Rheumatism.
3. Gout.
4. Hypertension.
5. Anti-inflammatory.
6. Antipyretic.
7. Analgesic.
8. Local anesthetic.

Toxicity

• At the toxic doses, the victim feels tingling in the lips, the tongue, the throat, then the face and limbs. Anguish (كرب, غم, hardship, misery, suffering), dizziness, myasthenic weakness, numbness, chills, rashes and diarrhea as well as cardiac system alterations.

• Death occurs by respiratory arrest while the subject remains fully conscious, (similar to coniine toxicity of *Conium maculatum*).

• *Aconitum*: herbaceous perennial plants are chiefly native to the mountainous parts of the northern hemisphere.
Delphinium:

- Is a genus of about 300 species of perennial flowering plants in the family Ranunculaceae, native throughout the Northern Hemisphere and also on the high mountains of tropical Africa.
- All members of the *Delphinium* genus are toxic to humans and livestock.
- Death is through **cardiotoxic** and **neuromuscular blocking** effects, and can occur within a few hours of ingestion.

- **All parts** of the plant contain various **diterpenoid** alkaloids, typified (represented or symbolized) by **methyllycaconitine**, so they are very poisonous.
2. Alkaloids with C-19 carbon atoms:
- Atisine and viatichine.
- Diterpene alkaloids.
- These are less toxic than aconite alkaloids.

Annona squamosa

Monoterpenic alkaloids

- **Gentianine:**
  - This alkaloid is found in *Gentiana* species

  **Pharmacological effects:**
  1. CNS stimulant.
  2. Hypotensive.
  3. Anti-inflammatory.
  5. Tonic (strengthening and refreshing effect).
➢ Generic name: **paclitaxel**.
➢ Obtained from **Taxus brevifolia** tree. (bark of stem).

Taxol

➢ Collected from USA on the pacific ocean. The mature tree is 100 years old.

➢ **Problem:** the plant yield is very small, 12 kg of bark yield 0.5 gm of taxol.

➢ To overcome this problem of the low yield:

1. The European species **Taxus baccata** that is known to yield considerable amounts of **10-deacetylbaccatin III** (precursor for the anti-cancer drugs). This compound is then converted to taxol.

2. Also, by tissue culture.
It is active for solid tumors, leukemia and melanoma cell line.

Taxol was marketed by Bristol Myers Squibb for:
1. Ovarian cancer.
2. Breast cancer.

Mode of action: prevents the mitotic spindle from being broken down by stabilizing microtubules bundles during cell division.

Paclitaxel
- a potent cytotoxic agent
- mechanism of action
  - interferes with mitotic spindle function
    - enhancing the rate and yield of microtubule assembly
    - preventing microtubule depolymerization
  - block the cell in the G2/M phase of the cell cycle
  - ↑ apoptosis and tumor reoxygenation also may occur

Anticancer drugs: Mechanism of Action of Taxol

Taxol promotes the polymerization of tubulin heterodimers to microtubules. At clinically relevant concentrations, taxol binds to microtubules resulting in their stabilization via suppressing their dynamic changes. Taxol thus interferes with the formation of mitotic spindle, which causes the chromosomes not to segregate, and consequently mitotic arrest.
• **Docetaxel:**
  - Is more water-soluble than paclitaxel.
  - A semi-synthetic drug from 10-deacetylbaccatin.
  - It also works as paclitaxel by stabilizing the microtubules.
  - Used as a single agent against **breast cancer** that is resistant to other agents or which has recurred after treatment.

*Taxus baccata*