JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Natural Products: AS a Classical and Adavance Theraptic

Dr. Mala Kumari
Associate Professor
Department of Chemistry, Satish Chandra College, Ballia(U.P.)

Abstract

Natural products have played a significant role in drug discovery and development. Natural products continue to be a rich source of potential drugs. While not all approved drugs are directly derived from natural products, many successful medications have their origins in natural compounds. The process of natural products-based drug discovery and development involves several steps like extraction, isolation, and characterization of natural products or their metabolites. Design, synthesis, and evaluation of synthetic or semi-synthetic derivatives or analogs. Development of purely synthetic molecules inspired by natural products. Researchers aim to bridge the gap between natural product chemical structures and their biological effects, ultimately benefiting patients with innovative therapies. Natural products remain a valuable resource for drug discovery, and ongoing research promises exciting developments in drug, here some natural product viz. Morphine, Heroin, Quinine , Cocaine, Nicotine And Respinre are disused for their medicinal importance

Key words: Natural product, drug, medicine, morphine, heroin and alkaloids

1. Introduction

Alkaloids exert **remarkable physiological effects** on humans and other animals. They serve as the **active components** in numerous medicinal plants and plant-derived drugs. Alkaloids exhibit **diverse structures** and a wide range of **physiological activities,** their uniqueness sets them apart from other natural product groups. **Common Alkaloids** like **Atropine**, **Strychnine, Caffeine**, **Nicotine**, **Morphine**, **Codeine**, **Cocaine**, respirine and more. Naturally occurring receptors for alkaloids that have been identified in humans and animals, suggests an **evolutionary role** for alkaloids in physiological processes. Alkaloids are **relatively more stable compounds**. They accumulate as end products of **biosynthetic pathways**, often starting from common amino acids (e.g., lysine, ornithine, tyrosine, tryptophan)1.

Color and Taste:

Alkaloids are usually **colorless**, but some are colored like:

- **Berberine**: Yellow
- **Sanguinarine salt**: Copper-red
- **Betanidin**: Red

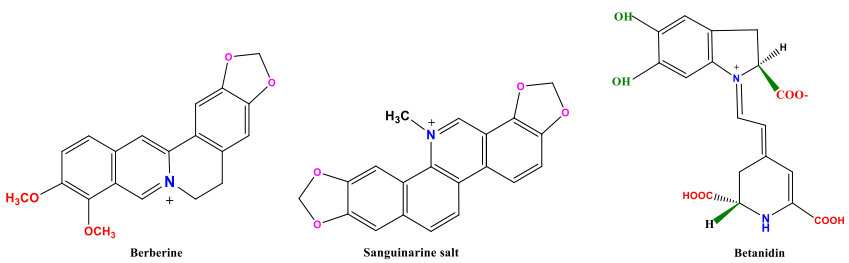


Figure 1. Structural Classification of Flavonoids

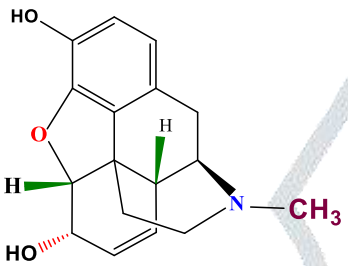
Interestingly, they almost always taste bitter.

Solubility and Oxygen Content:

Alkaloids may exist in free form, as salts, or as N-oxides. Most alkaloids contain **oxygen**, but some, like **coniine** (from hemlock) and **nicotine** (from tobacco), are oxygen-free.

The diverse structures alkaloids, physiological effects, and evolutionary significance continue to intrigue scientists and researchers. From ancient medicinal uses to modern drug discovery, alkaloids play a crucial role in our understanding of nature and health. Continue to be a captivating area of study, offering insights into both natural processes and potential therapeutic applications.

MORPHINE



Morphine

Morphine is a potent **opiate** found naturally in **opium**, which is derived from the dried latex of opium poppies(Papaver somniferous))

PURPOSE USES: Morphine is primarily used as an **analgesic** (pain medication) to manage moderate-to-severe acute and chronic pain caused by various conditions2-4.

1. **Administration**: There are several methods to administer morphine:
- **Oral**: Taken by mouth.
- **Sublingual**: Placed under the tongue.
- **Inhalation**: Smoked.
- **Injection**: Intramuscular, subcutaneous, or intravenous.
- **Transdermal**: Applied through the skin.
  Rectal Suppository: Inserted rectally.
2. **Mechanism of Action**: Morphine acts directly on the **central nervous system (CNS)** to induce analgesia and alter perception and emotional response to pain. It binds to mu-opioid receptors in both the CNS and the peripheral nervous system (PNS)[13].
3. **Dependence and Tolerance**: Physical and psychological dependence, as well as tolerance, may develop with repeated administration of morphine.
4. **Uses**:

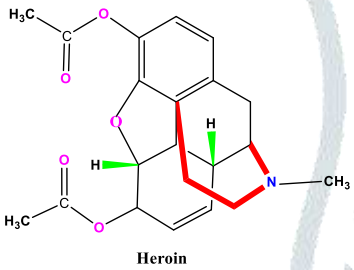
- **Acute Pain**: Morphine can be taken for both acute and chronic pain. It is frequently used for pain related to conditions such as **myocardial infarction**, **kidney stones**, and during **labor**.
- **Duration**: Its maximum effect is reached after about **20 minutes** when administered intravenously and **60 minutes** when administered orally. The duration of its effect is **3–7 hours**.

Morphine, a powerful **analgesic opioid**, has been used for pain relief and other medical purposes for many years. Here are some essential medicinal uses of morphine:

1. **Relief of Pain from Heart Attacks (Myocardial Infarction)**: Morphine is crucial in managing the severe and excruciating chest pain associated with heart attacks. It helps ease the pain and alleviate symptoms like apprehension and a feeling of heaviness over the chest, which can further stress the heart[1].
2. **Sickle Cell Crisis**: Morphine provides relief from the intense bone and joint pain experienced during sickle cell crises.
3. **Surgical Pain Management**: Morphine is administered before, during, and after major surgeries, especially those involving bones and large organs.
4. **Anesthesia**: It is used for general anesthesia to sedate patients and for regional anesthesia (such as spinal or epidural anesthesia).
5. **Severe Injuries**: Morphine helps manage pain caused by severe injuries, such as those resulting from road traffic accidents.

6. **Renal Colic and Kidney Stones**: It provides relief from the pain associated with kidney stones as they pass through and obstruct the urinary pathway.
7. **Pulmonary Edema**: Morphine is used to relieve pain in cases of water accumulation in the lungs due to acute left ventricular failure or severe heart failure.
8. **Joint Pain from Rheumatoid Arthritis and Osteoarthritis**: Morphine helps alleviate severe joint pain caused by disabling diseases.
9. **Terminal Cancer Patients**: As part of palliative care, morphine is given to cancer patients with advanced disease to manage pain at the end of life.
10. **Cough Suppression**: Although there are less addictive alternatives, morphine can act as a cough suppressant when severe coughing is present.
11. **Relief from Severe Diarrhea**: Again, there are other opioids better suited for this purpose, but morphine can be used to manage severe diarrhea[1].
12. Since the 1920s, modern medicine and pharmaceuticals have advanced. During the 1940s, synthetic and semi-synthetic opioids — meaning they were completely developed through a chemical process or were created from chemical changes to the original opium plant — started to emerge. Although morphine is still used in clinical practice, there are now several opioids that are significantly more powerful, some of which are synthetic or semi-synthetic. However, morphine is still the standard by which pain relievers are measured. For example, hydromorphone (a semi-synthetic opioid) is "4 times stronger than morphine."
13. Today, laws and guidelines around morphine and all opioids continue to evolve. With new guidelines for patient care and higher awareness of opioid addiction, morphine can be a safe pain relief tool in a clinical setting.

Heroin chemical structure:



Heroin

Chemical Formula: $C_{21}H_{23}NO_5$

IUPAC/Systematic name :(5α, 6α)-7, 8-didehydro-4, 5-epoxy-17-methylmorphinan-3, 6-diol diacetate

Primary metabolites: The primary metabolites of heroin include 6-monoacetylmorphine, morphine, morphine-3-glucuronide, and morphine-6-glucuronide

Similarity to morphine: The heroin chemical structure is similar in many way to morphine and 6-acetyl morphine

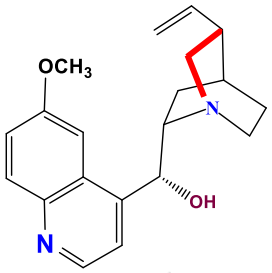
Heroin, is also known as diacetylmorphine or dimorphine ,is highly addictive opiod drug synthesized from morphine, which is a neutral substance extracted from the seedpod of opium poppy plant, **Papaver somniferum**. It is mainly used as a recreational drug for its euphoric effects. Heroin can be found in several forms ,including white and brown powder and black sticky substance known as black heroin. The transformation of morphine into heroin involves a chemical process called acetylation, which increases the potency of the drug5&6. While heroin was used for medical purposes due its effectiveness in reducing pain, it was later found to have a high potential for addiction and abuse, leading to serve health issues and societal problems. Today, heroin is classified as an illegal substance in many countries, and its use is associated with serious legal and health risks. The drug is known for causing both physical and psychological dependence, and long-term use can be lead to devastating consequences for individuals and communities. It's important to be aware of the dangers of heroin and to seek help if you or someone you know is struggling with addiction7,8 &9.

Today Morphine is generally safe when used in clinical settings

Indeed, in 1874, heroin was introduced with the intention of serving as a cure for morphine addiction. This was during a time when the addictive properties of morphine were well-known, and there was a significant need for a less addictive alternative for pain relief. Heroin, or diacetylmorphine, was synthesized by chemist Alder Wright by combining morphine with other chemicals. Initially, it was believed that heroin would be a safer, non-addictive substitute for morphine. However, it soon became apparent that heroin was actually more potent and had a higher potential for addiction than morphine. Despite its early use as a treatment for morphine addiction, heroin's use quickly led to its own patterns of abuse and addiction.BY the early 20th century, the medical community recognized the dangers of heroin, and its use became regulated. This historical attempt to use heroin as a solution to morphine addiction is a stark reminder of the complexities involved in understanding and treating substance dependence.

QUININE

The **quinine plant**, also known as **Cinchona Officinalis** or **Peruvian Bark**, is native to South America. It's a small tree that can grow up to **20 meters tall** in its natural habitat, but it can be pruned down and grown indoors as well. This evergreen tree produces small **white or pink flowers** that bloom throughout the year[4].**Quinine** itself is an alkaloid, a naturally occurring chemical compound. It was first isolated in **1820** from the bark of a **cinchona tree**, which is native to **Peru**. The molecular formula of quinine was determined by **Adolph Strecker** in **1854**[1]



Quinine

-**Structure**

- **Chemical Formula**: $C_{20}H_{24}N_2O_2$
- **IUPACName**:(6-Methoxyquinolin-4-yl)[(1S,2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol
- **Molar Mass**: 324.424 g/mol
- **Melting Point**: 177°C (351°F)

Chemical components:

1. **Aromatic Component**: Quinine contains a quinoline ring with a methoxy substituent.
2. **Amine Component**: The amine portion has a quinuclidine skeleton.
3. **Methylene Bridge**: The bridge connecting the two components has a hydroxyl group.
4. **Substituent at Position 3**: A vinyl group is attached at the 3 position.Quinine Structure

Interestingly, quinine is also used as an ingredient in **tonic water**, imparting that characteristic **bitter taste** Quinine, derived from the bark of the cinchona tree, has been used for various medicinal purposes.

Medicinal Use:

Malaria and **babesiosis**. Quinine is used to treat **malaria** and **babesiosis**. It's particularly effective against **Plasmodium falciparum** malaria strains that are resistant to chloroquine when **artesunate** is not available, It effectively kills the malaria-causing parasite and prevents the infection from spreading.

1. **Leg Cramps**: Some people believe that quinine can help with **nighttime leg cramps**. However, further research is needed to confirm its effectiveness in this regard[2].
2. **Restless Legs Syndrome (RLS)**: Although not conclusively proven, some individuals use quinine-containing tonic water to alleviate symptoms of **restless legs syndrome**.
3. **Bitter Taste in Tonic Water**: Quinine imparts a bitter taste to **tonic water**, which contains small amounts of this compound. Manufacturers add quinine to tonic water, making it a popular mixer for beverages[2].
4. **Safety and Allergies**:

- Quinine is generally considered safe in small doses. The FDA approves up to **83 parts per million** of quinine in carbonated beverages.
- People with **allergic reactions** to quinine should avoid tonic water and other products containing it.
- Individuals who are **pregnant or breastfeeding**, have **abnormal heart rhythms**, or suffer from **liver or kidney disease** should avoid quinine in medications[2].

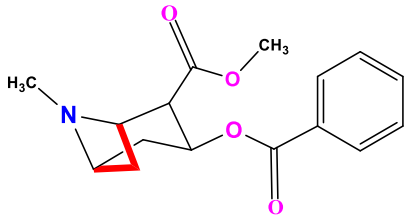
5. **Drug Interactions**: Quinine may interact with certain medications, including antidepressants, antacids, statins, blood thinners, and seizure medications. Consult a doctor before taking any medication or supplements containing quinine[2].

1. **Side Effects**: Common side effects include **headache**, **ringing in the ears**, **vision issues**, and **sweating**. More severe side effects can include **deafness**, **low blood platelets**, and an **irregular heartbeat**. Use of quinine can also make one more prone to **sunburn**[1].

2. **Mechanism of Action**: How quinine works as a medicine is not entirely clear. It's an important anti-fever agent and is especially useful in the prevention and treatment of malaria. Other alkaloids extracted from the cinchona tree include **cinchonine**, **cinchonidine**, and **quinidine**[3].

COCAINE

Cocaine *(Leaves Erythroxylin coca).*



Cocaine

Cocaine is the main psychoactive ingredient of the leaves of the plant Erythroxylin coca. Most of the **E. coca** is grown in three countries in South America, has a fascinating history that spans centuries. The chemical can be isolated from the leaves, and used in its chemical form. US is the number 1 consumer of cocaine in the world.

Much of the cocaine use is illegal and for recreational purposes. Cocaine is a very well known drug of abuse. It is generally considered to have some of the highest risks among the common drugs of abuse. Cocaine has a very high toll on society, as chronic use can cause a variety of health problems1,11 &12.

History of Cocaine

Ancient Use by Indigenous People:

- As far back as 3,000 BC, the Incas of the Andean region in South America used coca leaves, which contain cocaine, for their stimulating effects.
- Indigenous people in the Amazon Rainforest and Andes Mountains would chew coca leaves to experience an energetic high.
- European Discovery and Isolation
- In the 1850s, European scientists first isolated cocaine from coca leaves. German chemist Albert Niemann played a pivotal role in this discovery.
- Around the same time, French chemist Angelo Mariani created a tonic called Vin Mariani, blending Bordeaux wine with coca leaves. Advertisements touted it as a health-restoring elixir1

European Discovery and Isolation:

- In the 1850s, European scientists first isolated cocaine from coca leaves. German chemist Albert Niemann played a pivotal role in this discovery.
- Around the same time, French chemist Angelo Mariani created a tonic called Vin Mariani, blending Bordeaux wine with coca leaves. Advertisements touted it as a health-restoring elixir1

Medical Marvel and Addiction

- Carl Koller, an Austrian ophthalmologist, experimented with cocaine as a surgical anesthetic. Ether and chloroform caused vomiting during delicate eye surgeries, so Koller soaked eyes in a cocaine solution. Patients no longer flinched when the scalpel touched their eyes.
- Pharmaceutical companies began marketing cocaine as an anesthetic. However, accidental overdoses during surgery led to a decline in enthusiasm for its medical use.
- Sigmund Freud, the founder of psychoanalysis, was fascinated by cocaine. He experimented with it early in his career and even wrote a paper titled "Uber Coca," praising its effects. Unfortunately, Freud struggled with cocaine addiction for 12 years.

Cocaine and Coca-Cola:

- In 1886, American pharmacist John Stith Pemberton created Coca-Cola, a beverage infused with cocaine and sugary syrup. Interestingly, this drink didn't contain alcohol.
- Initially, soda machines were only found in pharmacies. However, when government regulations banned cocaine, it was removed from Coca-Cola, marking the end of its cocaine-infused era1

Cocaine structure (Richard Willstätter in 1898.)

- **IUPAC Name**: Methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate
- **Molar Mass**: 303.358 g/mol
- **Melting Point**: 98°C (208°F)
- **Boiling Point**: 187°C (369°F)

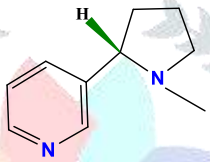
Structural Components:

- **Aromatic Component**: Cocaine contains a **quinoline ring** with a **methoxy substituent**.
- **Amine Component**: The amine portion has a **quinuclidine skeleton**.
- **Methylene Bridge**: The bridge connecting the two components has a **hydroxyl group**.
- **Substituent at Position 3**: A **vinyl group** is attached at position 3.

Cocaine acts as a central nervous system (CNS) stimulant .

Nicotine

Nicotine is a the chief naturally alkaloid that found in tobacco plant.



Nicotine

•IUPAC name 3-(1-methyl-2-pyrrolidinyl) pyridine.

•It is a bicyclic compound with a pyridine cycle and a pyrrolidine cycle. The molecule possess an asymmetric carbon and so exists in two enantiomeric R and S compounds 13.

• It occurs in the plant leaves as salts of malic acid and citric acid to the extent of 4 to 5 percent. The alkaloid was named after the **Frenchman NICOT** who introduced tobacco in France in 1560.14

History of Nicotine

Nicotine is an organic compound that is the principal alkaloid of tobacco. It's named after the tobacco plant **Nicotiana tabacum**, which in turn is named after **Jean Nicot**, a French ambassador to Portugal. Jean Nicot sent tobacco seeds to Paris in 1550.

The history of nicotine is quite interesting:

- The tobacco plants, from which nicotine is derived, originated in South America before spreading to North America, Africa, and Australia. Native people of these areas originally used the leaves of tobacco plants to chew, smoke, or use in religious rituals.
- Crude nicotine was known by 1571.
- The compound was obtained in purified form in 1828.
- The correct molecular formula was established in 1843.
- The first laboratory synthesis was reported in 1904.

Nicotine occurs throughout the tobacco plant and especially in the leaves. The compound constitutes about 5 percent of the plant by weight. In its pure state, it is a colourless, odourless liquid with an oily consistency, but when exposed to light or air, it acquires a brown colour and gives off a strong odour of tobacco.

Nicotine is the chief addictive ingredient in the tobacco used in cigarettes, cigars, and snuff. It has a unique biphasic effect; when inhaled in short puffs it has a stimulant effect, but when smoked in deep drags it can have a tranquilizing effect. In larger doses, nicotine is a highly toxic poison that causes vomiting and nausea, headaches, stomach pains, and, in severe cases, convulsions, paralysis, and death.

Today, nicotine is commercially obtained from tobacco scraps and is used as an insecticide and as a veterinary vermifuge. Nitric acid or other oxidizing agents convert it to nicotinic acid, or niacin, which is used as a food supplement. Neonicotinoids, also called neonics, are a class of synthetic systemic insecticides that are chemically related to nicotine.

Medicinal uses

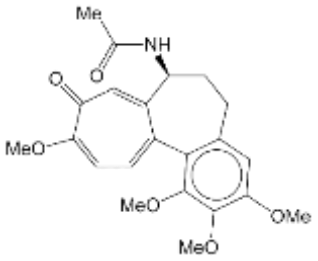
Nicotine, a naturally occurring alkaloid found in tobacco and other nightshade plants, is often associated with smoking and its harmful effects. However, beyond its role in cigarettes, nicotine has surprising **medicinal properties**. Let's explore some of its positive effects3&4:

1. **Increased Neurotransmitters**:
   - Nicotine imitates acetylcholine and binds to **nicotinic acetylcholine** receptors in the brain.
   - This promotes the release of neurotransmitters like **dopamine, serotonin, and acetylcholine**, which play crucial roles in cognitive functions, mood regulation, and stress management.
2. **Antidepressant Properties**:
   - Nicotine affects neural pathways related to an individual's frame of mind.
   - It can reduce stress and improve mood by stimulating the central nervous system and altering brain waves.
   - Some medical professionals even prescribe nicotine as an antidepressant15.
3. **Neuroprotective Properties**:
   - Research suggests that nicotine may protect neurons from degeneration.
   - By affecting nicotinic acetylcholine receptors and reducing estrogen levels, nicotine exhibits neuroprotective effects.
4. **Treatment for Schizophrenia**:
   - Nicotine can improve cognitive problems associated with schizophrenia.
   - It enhances memory, learning ability, and other functions, contributing to mental stability for many schizophrenic individuals.
5. **Management of Attention-Deficit Hyperactivity Disorder (ADHD)**:
   - Studies from the 1990s indicate that nicotine may help manage ADHD.
   - It improves concentration, reduces reaction time, and increases vigor in subjects.
6. **Potential Role in Alzheimer's Disease**:
   - Ongoing research explores nicotine's ability to enhance brain function.
   - While caution is necessary due to its addictive nature, nicotine shows promise in reducing the effects of Alzheimer's disease .

Note: That nicotine is not without risks, especially when associated with smoking. Chronic nicotine use is linked to various health issues, including cancer, hypertension, and cardiovascular diseases. However, in controlled forms such as nicotine gums or patches, it can offer unexpected health benefits. Always consult a healthcare professional before using nicotine for any medicinal

Reserpine

Reserpine was isolated in 1952 from the dried root of Rauwolfia serpentina (Indian snakeroot), which had been used for centuries in India for the treatment of insanity, fever, and snakebites



Reserpine

History of reserpine,

Strctures of all the scalton of naturally occouring

a compound with a fascinating journey:

1. **Discovery and Isolation**:
   - In **1952**, reserpine was isolated from the dried root of **Rauvolfia serpentina**, also known as **Indian snakeroot** or **Sarpagandha**.
   - This plant had been used for centuries in India for various purposes, including treating **insanity**, **fever**, and **snakebites**.
   - Interestingly, even **Mahatma Gandhi** used it as a tranquilizer
2. **Medical Applications**:
   - **Reserpine** found its way into medicine and was introduced in **1954**, just two years after **chlorpromazine**.
   - Historically, the powdered whole root of Rauwolfia serpentina was used to treat conditions such as **snakebites**, **insomnia**, **hypertension** (high blood pressure), and **insanity16&17**.

- As a drug, **reserpine** is primarily used for treating **high blood pressure** (hypertension). It is often combined with a **thiazide diuretic** or **vasodilator**.
- Large clinical trials have demonstrated that combining **reserpine** with a **thiazide diuretic** can reduce mortality in people with hypertension.
- Its antihypertensive effects stem from its ability to deplete **catecholamines** (including norepinephrine) from peripheral sympathetic nerve endings, thus impacting heart rate, cardiac contraction force, and peripheral vascular resistance.
- At low doses (0.05 to 0.2 mg per day), **reserpine** is generally well tolerated, with nasal stuffiness being the most common adverse effect.
- Interestingly, it has also been used for **relief of psychotic symptoms**.

Toxic effect of reserpine

Reserpine, while valuable in medicine, does come with some **potential adverse effects**. Let's explore them:

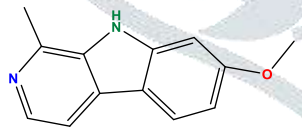
1. **Nasal Congestion**: Reserpine can cause nasal congestion, leading to stuffiness or discomfort in the nasal passages.
2. **Gastrointestinal Effects**:
- **Nausea** and **Vomiting**: Some individuals may experience nausea and vomiting after taking reserpine.
- **Gastric Intolerance**: Increased cholinergic activity in gastric tissue can lead to gastric intolerance.
- **Gastric Ulceration**: Reserpine may impair mucosal quality, potentially causing gastric ulceration.
- **Stomach Cramps** and **Diarrhea**: These gastrointestinal symptoms are also associated with reserpine use.
3. **Cardiovascular Effects**:
- **Hypotension**: Reserpine can cause low blood pressure (hypotension).
- **Bradycardia**: It may also lead to a slower heart rate (bradycardia).
- **Worsening of Asthma**: Reserpine has the potential to exacerbate asthma symptoms.
4. **Psychiatric Effects**:
- **Mental Depression**: High doses of reserpine may cause significant mental depression.
- **Anxiety or Psychosis**: Anxiety or psychosis can occur as adverse effects.
5. **Other Considerations**:
- Some formulations of reserpine may contain **tartrazine**, which is important to be aware of.

Notable: that these effects can vary from person to person, and it's essential to consult a healthcare professional if you experience any unusual symptoms while taking reserpine

Reserpine emerged from ancient roots, found its place in medicine, and continues to play a role in managing hypertension. Its journey is intertwined with cultural practices, historical uses, and scientific discovery.

Harmine compound with a rich history, has been used for various purposes.

M**olecular formula** :$C_{13}H_{12}N_2O$



Harmine

It is a **beta-carboline** and a **harmala alkaloid**, occurring in several plants, most notably **Syrian rue** and **Banisteriopsis caapi**. Harmine **reversibly inhibits monoamine oxidase A (MAO-A)**, an enzyme responsible for breaking down monoamines, making it a **reversible inhibitor of monoamine oxidase A (RIMA)**. Notably, it does not inhibit MAO-B. Some other names for harmine include **banisterin**, **banisterine**, **telopathin**, **telepathine**, **leucoharmine**, and **yagin**. If you're interested in its biosynthesis, the exact precursor (whether free tryptamine or L-tryptophan) remains uncertain, but it is postulated that L-tryptophan is the most likely precursor, with tryptamine as an intermediate in the pathway. The proposed biosynthetic scheme involves several steps, including decarboxylation, rearrangements, and hydroxylation 18.

1. **Origin and Traditional Use**:

- **Harmine** is a **beta-carboline alkaloid** found in several plants, most notably the **Syrian rue** (*Peganum harmala*) and **Banisteriopsis caapi**.
2. For thousands of years, it has been employed in Middle Eastern and Chines traditional medicine. **Pharmacological Activities**:
- **Anti-Inflammatory**: Harmine exhibits anti-inflammatory effects.
- **Neuroprotective**: It has properties that protect nerve cells.
- **Antidiabetic**: Harmine shows potential in managing diabetes.
- **Antitumor**: Scientific studies indicate its antitumor properties.
3. **Antioxidative:** It acts as an antioxidant, combating oxidative stress
4. **Monoamine Oxidase Inhibition**:
- **Harmine reversibly inhibits monoamine oxidase A (MAO-A)**, an enzyme responsible for breaking down monoamines.

- As a **Reversible Inhibitor of Monoamine Oxidase A (RIMA)**, it affects neurotransmitter levels19.
- Notable , harmine does not inhibit MAONotably, harmine does **not inhibit MAO-B**

5. **Safety Considerations**:

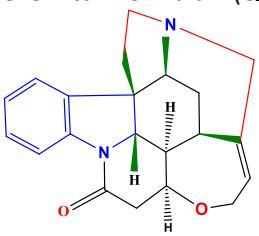
- Oral or intravenous harmine doses ranging from **30 to 300 mg** may cause **agitation**, **bradycardia or tachycardia**, **blurred vision**, and **hypotension**.

- It's essential to approach harmine with caution due to its potent effects.

While harmine's historical use has been diverse, its current exploration focuses on its potential therapeutic benefits.

Strychnine

Chemical formula: ($C_{21}H_{22}N_2O_2$) is a potent alkaloid produced by **Strychnos species**, particularly **S. nux-vomica[20]**.



Strychnine

Properties

1. **Historical Context**:

- **Discovery**: French chemists **Joseph-Bienaime Caventou** and **Pierre-Joseph Pelletier** identified strychnine in **1818**.
- **Plant Source**: It originates from the seeds of the **nux vomica tree** (Strychnos nux vomica), native to **India**.
- **Traditional Names**: The seeds have been historically known as "poison nuts" or "Quaker buttons."

2. **Medicinal Use**:

In the past, strychnine was used in small doses for various purposes:

- **Muscle Stimulation**: It acted as a **heart and bowel stimulant**.
- **Performance Enhancement**: Some used it for performance enhancement[21&22].

However, due to its **extreme toxicity**, it is **no longer used medicinally**.

3. **Chemical Challenges**:

- Isolating strychnine from nux vomica seeds was complex.
- Determining its chemical structure posed challenges.
- Achieving total synthesis of strychnine was a formidable goal for chemists.

4. **Natural-Product Chemistry**:

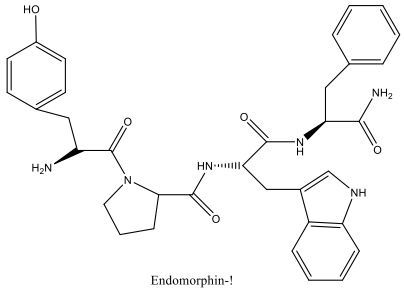
- Strychnine's isolation marked the beginning of true **natural-product chemistry**.
- Other early active ingredients isolated from plants include **morphine**, **narcotine**, **veratrine**, **colchicine**, and **caffeine**.

While strychnine's medicinal use has faded, its historical significance remains a testament to scientific curiosity and innovation.

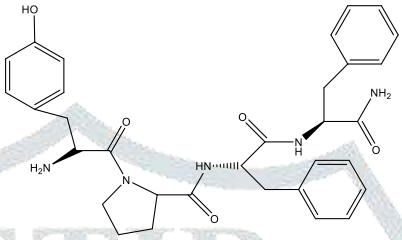
I**nnovative drugs** some drugs that have emerged from the inspiration of natural products like **morphine**, **quinine**, **cocaine**, **nicotine**, and the mysterious **respirine**:

1. **Endomorphin Variants**: Scientists have engineered variants of **endomorphin**, a naturally occurring chemical in the body. These variants exhibit pain-killing properties similar to **morphine**, but without the unwanted side effects. Imagine a potent analgesic that doesn't compromise respiratory function or cause constipation.
2. **Casgevy (CRISPR Treatment)**: Initially approved for **sickle cell anemia**, Casgevy is now under review by the FDA for another genetic blood disorder called **beta thalassemia**. This gene-editing therapy allows people to produce more healthy blood cells, reducing painful episodes associated with these conditions[1].

3. **Gene-Based Treatments for Hemophilia B**: Pfizer has developed a gene therapy that provides the missing coagulation factor for patients with **hemophilia B**. In studies, this therapy significantly lowered the risk of annual bleeding episodes[1]



Endomorphin-!



4. Endomorphin-2

5. .**Karuna Therapeutics' Schizophrenia Drug**: A groundbreaking treatment for **schizophrenia**, this drug targets different brain receptors than existing antipsychotics. By focusing on muscarinic receptors, it aims to reduce the extremes of symptoms typical of this psychiatric condition[1].

6. The recent developments related to drugs derived from heroin are primarily focused on the rise of synthetic opioids, particularly **fentanyl**. Fentanyl is a synthetic opioid that is **50 to 100 times more powerful than morphine**[5]. It has been found in many other illegal drugs, including heroin, often without the users' knowledge, which has contributed to a significant increase in overdose deaths[5].

7. Since 2013, fentanyl has been made in underground laboratories and mixed into the heroin supply in North America. This shift occurred as crackdowns on heroin led suppliers to produce fentanyl because it is easier to smuggle and avoid detection[3]. The UN Office on Drugs and Crime (UNODC) reported that opioids, which include both heroin and legal pain relievers, were responsible for around two-thirds of drug-related deaths in 2017[1].

8. The misuse of synthetic opioids like fentanyl is an ongoing crisis, particularly in the US and Canada, with over 51,000 overdoses reported in 2017[5]. Additionally, countries in West, Central, and North Africa are experiencing an opioid crisis surrounding another drug, **Tramadol**, which has flooded the market in recent years[1].

9. It's important to note that while these drugs are derived from or related to heroin, they are distinct substances with their own profiles of effects and risks. The increased potency of synthetic opioids has led to a higher risk of overdose and death, making them a significant public health concern.

While these drugs may not directly bear the names of their natural predecessors, they owe their existence to the insights gained from compounds like morphine, quinine, cocaine, and nicotine. The journey from plant-derived inspiration to cutting-edge therapies continues to shape the landscape of modern medicine.

References

1. National Institute on Drug Abuse (NIDA) Heroin
2. Brouillard, R.; Dangles, O. The Flavonoids: Advances in Research Since 1986; Harborne, J. H., Ed.; Chapman and Hall: London, 1993; pp 565–588.
3. Harborne, J. B.; Baxter, H. The handbook of natural flavonoids, Vols. 1 and 2, John Wiley and Sons, Chichester, UK, 1999.
4. The Science of Flavonoids; Grotewold, E., Ed.; Springer: New York, 2006.
5. Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67-202 and reference cited therein.
6. Zhuang, C.; Zhang, W.; Sheng C.; Zhang, W.; Xing, C.; Miao, Z. Chem. Rev. 2017, 117, 7762-7810.
7. (a) Subramanian, R. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 6797; (b) Subramanian, R. S.; Balasubramanian, K. K. *Synthetic Commun.* **1989**, 19, 1255.
8. (a) Wang, L.; liu, X.; Dong, Z.; Fu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2008**, *47*, 8670-8673; (b) Wang, H. F.; Xiao, H.; Wang, X. W.; Zhao, G. *Tetrahedron* **2011**, *67*, 5389-5394.
9. Kavala, V.; Lin, C.; Kuo, C. W.; Fang, H.; Yao, C. F. *Tetrahedron* **2012,** *68*, 1321-1329.
10. Shi, L.; Feng, X. E.; Cui, J. R.; Fang, L. H.; Du, G. H.; Li, Q. N. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5466–5468.
11. Mondal, R.; Gupta, A. D.; Malik, A. K. *Tetrahedron Lett.* **2011**, 52, 5020-5024.

12. (a) Chen, P. Y.; Wang, T. P.; Chiang, M. Y.; Huang, K. S.; Tzeng, C. C.; Chen, Y. L.; Wang, E. C. *Tetrahedron* **2011**, *67*, 4155-4160; (b) Manivel; Rai, P.; Rai, N. P.; Jayashankara, V. P.; Arunachalam, P. N. *Tetrahedron Lett.* **2007**, *48*, 2701-2705.

13. Chandrasekhar, S.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2005**, *46*, 6991-6993.

14. Kumar, A.; Sharma, S.; Tripathi, V. D.; Srivastava, S. *Tetrahedron* **2010**, *66*, 9445-9449.

15. Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369-1371.

16. Lee, J. I.; Jung, M. G.; Jung, H. J. *Bull. Korean Chem. Soc*. **2007**, *28*, 5859

17. Spearing, P.; Majetich, G.; Bhattacharyya, J. *J. Nat. Prod.* **1997,** *60,* 399-400.

18. Cui, H.; Li, P.; Chai, Z.; Zheng, C.; Zhao, G.; Zhu, S. *J. Org. Chem.* **2009**, *74*, 1400-1402.

19. Bernini, R.; Mincione, E.; Provenzano, G.; Fabrizi, G.; Tempesta, S.; Pasqualetti, M. *Tetrahedron* **2008**, *64*, 7561-7566.

20. Ahmed, N.; Ali, H.; Van Lier, J. E. *Tetrahedron Lett.* **2005**, *46*, 253-256.

21. Korenaga, T.; Hayashi, K.; Akaki, Y.; Maenishi, R.; Sakai, T. *Org. Lett.* **2011**, *13*, 2022-2025.

22. Zhou, S.; Zhou, Y.; Xing, Y.; Wang, N.; Cao, L. *Chirality* **2011**, *23*, 504-506