

OPIUM AND ITS MAJOR ALKALOIDAL CONSTITUENTS: A REVIEW ARTICLE

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Abstract

Poppy (Papaver somniferous L.) is a member of the Papaveraceous family. It is indigenous of south east of Europe and Asia. It is cultivated all over the world and there is not any wild type of this species. It is widely grown as an ornamental flower throughout Europe, North America, South America, and Asia. Until now more than 40 different alkaloids have been known in this species which the most important ones are morphine, codeine, thebaine, papaverine and noscapine. Alkaloids are affected with genetical characteristics and environmental conditions. Poppy seeds are an important food item and the source of poppy seed oil, healthy edible oil that has many uses. The most important application of papaver alkaloids is due to their analgesic properties. Use of opium poppy (Papaver somniferum L.) as a medicinal plant has been described in the ancient literature of Indian system of medicine (Ayurveda).

Keyword: - *Opium, Alkaloids, Morphine, Codeine, Medicinal plants*

INTRODUCTION

The milky exudate obtained by incising the unripe capsules of *Papaver somniferum* L. or its variant *album* De Candolle is known as opium (Fam. Papaveraceae). It produces a minimum of 9.5 percent anhydrous morphine. Powdered Opium is Opium that has been dried to a fine powder at a temperature below 70°C. Anhydrous morphine yields not less than 10.0 percent and not more than 10.5 percent when powdered opium is used. With the exception of starch, it may contain any of the diluents allowed for powdered extracts. [1]. Opioids are a class of drugs used to suppress the central nervous system (CNS) [2]. This class is particularly well-known for its analgesic characteristics, which are used to manage pain in individuals suffering from chronic discomfort, such as cancer. Some opioids, such as codeine, have an antitussive action that is commonly used in medical practice. [3,4]. The most often cited uses of poppy in ancient medicine were as a sedative and an analgesic [5,6]. Opium is a more or less spherical, oval, brick-shaped or elongated, somewhat flattened mass with an average diameter of 8-15 cm and a weight of 0.3-2 kg. Externally, it has a gritty surface and is pale olive-brown or olive-gray in color. It may be covered with a thin covering of poppy leaf fragments or fruits of a *Rumex* species adhering to the packing. When it's new, it's plastic-like, but as it ages, it becomes denser and more durable. It's reddish brown and coarsely granular on the inside. Amorphous latex masses, leaf and epicarp fragments, dark stone cells, narrow spiral vessels or sections of vessels, parenchyma, starch grains, and refringent crystals can all be found in powdered opium. [7,8,9].

The opium poppy is an annual plant with an erect stem and a single white, red, or purplish bloom, depending on the cultivar. On incision, all portions of the plant ooze a white latex. The taxonomy of the genus *Papaver* is highly complicated, with around 100 species divided into nine to twelve divisions. The terms subspecies (ssp.) and varieties (var.) are used in this nomenclature, however there is a lot of morphological diversity because the opium poppy has been cultivated for so long. In brief, the genus' taxonomy is complex and unresolved, however for the purpose of clarity, the following distinctions may be useful. [7,10] The white poppy, which has white flowers and seeds, is widely grown in India and is known as the variety *album*. The poppy variation *nigrum*, which is notable for its purple blooms and slate grey seeds (sometimes known as "maw seeds"), is widely cultivated in Europe for its seed. The poppy, which is known for its purple petals and purplish-black seeds, is widely grown in Asia Minor and is known as the variety *glabrum*. [7].



Fig. 1: Opium

Opium production

The International Opium Commission was established in 1909 to control opium production, and by 1914, thirty-four governments had agreed that opium production and importation should be reduced. All signatory countries agreed to enact rules and regulations restricting the import, sale, distribution, export, and use of all narcotic medicines to medical and scientific purposes once the League of Nations took over this responsibility. The International Narcotics Control Board of the United Nations currently regulates the cultivation of the opium poppy on an international level, with India being the only country that produces enough opium to supply global demand. Although opium is produced in China and North Korea, this is reputed to be for exclusive domestic medical use. [10,11,12].

Production Of Opium

The cultivation of the opium poppy for the production of opium is primarily done in Madhya Pradesh, Uttar Pradesh, and Rajasthan in northern India. Like all poppies, the opium poppy requires rich, moist soil, plenty of sunlight, and a clear growing area. Poppy seeds are spread in well-cultivated fields in late fall or early winter (typically November). The fields are thinned once the plants emerge in the spring and reach a height of around 15 cm, with the remaining plants standing about 60 cm apart. Flowering takes place in April or May, with capsule maturation taking place in May or June. On average, each plant produces five to eight capsules, which change color from bluish-green to yellow as they ripen to around four centimeters in diameter. This is when the capsules are delicately incised horizontally (infrequently vertically) partially along their circumference one at a time, signaling the best moment for latex harvest. Workers step rearward to prevent direct contact with latex from the capsules that have just been incised, using a single three- to six-bladed knife or spiked tool. There are four to six of these incisions, each of which is cut deep enough to incise the lactiferous ducts but not so deep as to penetrate the endocarp, causing the latex to flow inward toward the capsule's core. Because these ducts (tubes)

open into one another, it is not required to incise all of them. When exposed to air, a white latex emerges from the incisions, quickly darkening to a brownish or blackish tint. Over the course of the next few days, each capsule may be incised four or five times. The darkened solidified latex is scraped away with an iron scoop/trowel or knife the morning after the incision, before the heat of the day causes the latex to become sticky. After gathering the necessary amount of latex, the material is kneaded into balls, wrapped in poppy leaves, and air-dried in the shade. Alternatively, the coagulated latex can be stored in perforated metal or clay pots, allowing a dark-colored fluid to drain. The pots are stored at a tilt and flipped over every 10 days for drainage if the bottoms are not perforated. Following that, the crude opium is placed in rectangular pans and let to sit in the sun for around 1-3 weeks at government collection locations. Each pan holds around 35 kg of opium and is stirred every 30 minutes with wooden paddles. During this time, the residual water content declines from around 30% to around 10%, and the material is then shaped into 5 kilograms cakes and delivered in polyethylene bags. [11,12,13].

Opium – Nonalkaloidal Constituents

Opium comprises about 5-20% water, about 20% carbohydrates, and a number of simple organic acids such as fumaric acid, lactic acid, oxaloacetic acid, and meconic acid. Meconic acid, a dibasic acid with a concentration of 3-5 percent, is easily recognized in solution (either in its unionized form or as its meconate) by the production of a deep red hue when ferric chloride solution is added, with the color remaining unchanged when weak hydrochloric acid is added. Although it was once thought that meconic acid was solely found in opium, it has now been discovered that several *Papaver* species that do not produce morphine but do produce other morphinan alkaloids include this dicarboxylic acid. Meconic acid is also found in several species of the *Papaveraceae* genera *Meconopsis* and *Roemaria*. As a result, the presence of this acid in a sample should be read more conservatively as a chemotaxonomic marker of the genus *Papaver* and other closely related taxa in the *Papaveraceae* family. [9,10].

OPIUM ALKALOIDS – AN OVERVIEW

Opium has a 10-20% alkaloid content, with more than 40 different alkaloids identified. The meconate (or other simple plant acid) salts of these weakly basic chemicals are found in plants. The morphinans morphine (8-17 percent), codeine (0.7-5 percent), and thebaine (0.1-2.5 percent); the benzylisoquinoline papaverine (0.5-1.5 percent); and the phthalideisoquinoline noscapine (narcotine) account for nearly all of the quantitative alkaloid content in opium (1-10 percent). Traces of other minor alkaloids exist and are represented by the following alkaloid classes: aporphines, protoberberines and tetrahydroprotoberberines, rhoeadines, benzophenanthridines, and tetrahydroisoquinolines [9,12].

Morphine

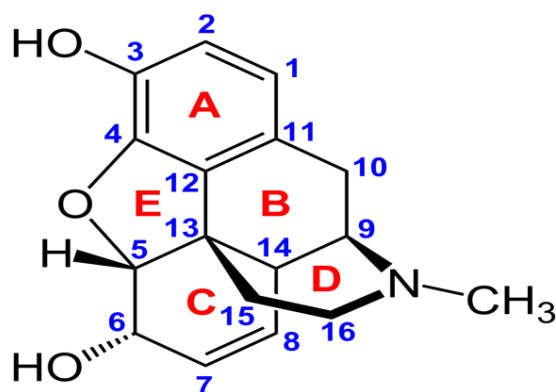
Morphine is a medicinally important chemical and the main component of alkaloid-rich latex in the opium poppy, which was initially discovered in *Papaver somniferum* opium. The majority of evidence suggests that Daniel Ludwig (1625–1680), Robert Boyle (1627–

1691), Jean-François Derosne (1774–1855), and Armand Séquin (1767–1835) were the first to extract morphine, but no one was able to identify or publish the results. [30,31]. In 1806 Friedrich Sertürner reported separating the active narcotic ingredient from opium, indicating that this active compound's molecular structure contains nitrogen, carbon, hydrogen, and oxygen. He was interested to see how his new finding would affect him. The novel substance was first tested on dogs, with Sertürner and three young volunteers consuming it, however one of the canines died during the trials. According to the findings, this new chemical, like opium, may ease pain while also providing euphoria. Addiction, psychological dependence, respiratory depression, nausea, vomiting, and constipation were all possible side effects. He called it a "vegetable alkali" and dubbed the white crystalline powder "morphium" after the Greek deity of dreams Morpheus. Despite the fact that Sertürner's study was disregarded for a decade, the results of his research were published in 1817 with the help of Joseph Louis Gay-Lussac, the French chemist who changed the word "morphium" to "morphine." Morphine was widely used as an analgesic in the 1830s, but its value skyrocketed in the 1850s after Charles-Gabriel Pravaz (1791–1853) and Alexander Wood (1817–1884) invented hypodermic needles. It also aided in the treatment of soldiers throughout the Crimean War (1853–1856), the American Civil War (1861–1865), and the Franco-Prussian War (1870–1871). Wilhelm Meissner (1792–1853), a German pharmacist, recognized the sort of material that Sertürner had extracted and proposed the generic word "alkaloid" for these alkaline herbal chemicals in 1818. Morphine was considered as the first successfully identified alkaloid [31-36].

Structure

Morphine 1 is made up of a benzene ring with a phenolic hydroxyl group at the C3 position and an alcohol hydroxyl group at the C6 position, as well as a nitrogen atom. The most crucial group for the affinity of the opioid receptor, which renders the substance chemically active, appears to be the tertiary form of nitrogen. Furthermore, chemical modifications to the aromatic ring have always resulted in a significant reduction of activity. To put it another way, the C3 phenolic hydroxyl group is critical for receptor engagement and biological action. The removal of the 3-OH group, for example, reduces analgesic action by tenfold. Because the morphine molecule possesses five chiral carbons and only the diastereoisomer (5R, 6S, 9R, 13S, 14R) is biologically active, it is commonly referred to as analgesic.

Natural morphine has a high activity because the hydroxyl group, tertiary amine, and aromatic ring interact with three binding sites in the receptor, whereas (+) morphine has only one contact due to its orientation in the enantiomer, making it a poor molecule as an analgesic. [26] In general, opioid medicines like morphine engage directly with opioid receptors, whereas other addictive substances like marijuana, alcohol, and nicotine indirectly activate endogenous opioid systems. [27,28].



Pharmacology. Because of its ability to bind to receptors ordinarily acted upon by endogenous opioids, morphine is a prototypical exogenous opioid (xenobiotic opioid) that generates a well-characterized analgesia, as well as certain other pharmacological activities. Other opium alkaloids, such as codeine, as well as semisynthetic opioids (oxycodone, oxycodone, hydromorphone, hydrocodone) and synthetic opioids (meperidine, methadone, fentanyl, pentazocine) are examples of exogenous opioids. Endogenous opioids are peptides that spontaneously bind to opioid receptors, and the name endorphin (endogenous + morphine) was developed to refer to the entire class of endogenous opioids, as well as a single endogenous opioid, μ -endorphin. The presence of opioid receptor binding sites in the brain was demonstrated in 1973 via the use of radioligand (radiolabeled opioid compounds) binding assays in which saturable binding of radioligands was observed. The bound radioligands could then be stereoselectively displaced by nonradiolabeled opioid compounds. The discovery of opioid-receptor multiplicity followed shortly afterward and the existence of three major types of opioid receptors [μ (μ), δ (δ), and κ (κ)] was established through receptor binding studies and cloning experiments. These receptors are members of the superfamily of G-protein-coupled receptors. [20,21,39].

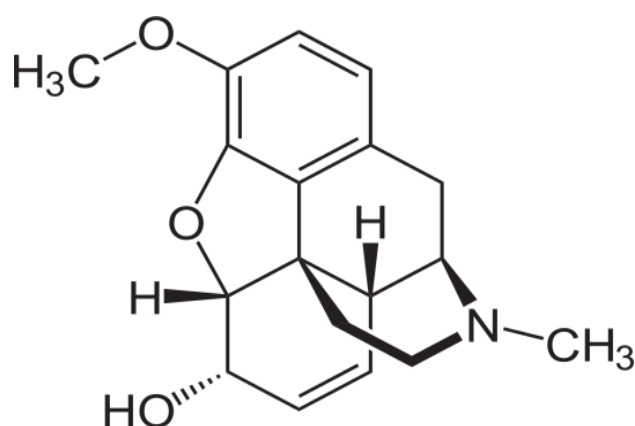
CODEINE

Robiquet extracted codeine, the 3-methylether of morphine, from Opium in 1833, and Grimaux methylated morphine for the first time in 1881. The structure of codeine was eventually elucidated as a result of the above-mentioned study by Robinson, School, and others, culminating in an important series of crucial degradations and rearrangements by Gulland and Robinson in 1925. Codeine is found in opium in concentrations ranging from 0.7 to 2.5 percent, and as such is not present in significant quantities for pharmaceutical manufacturing. As a result, codeine is commonly made by methylating morphine using a trimethylphenylammonium salt in xylene or xylene-methanol. [9,17].

Codeine (pK_b 5.8) is found in nature as orthorhombic rods or tablets in its levorotatory form. It creates water soluble salts with a variety of acids, the most common of which being phosphate and sulphate salts. Because it is around 10 times more water soluble than codeine sulphate, the phosphate salt is virtually exclusively employed in commercially available codeine formulations (18,19). The pharmacological effects of codeine are similar

to those of morphine; however, it is less strong. Analgesic codeine is used to treat mild to moderate pain as well as coughing caused by chemical or mechanical irritation of the respiratory system. Because of decreased first-pass hepatic metabolism, the alkaloid is roughly 60% as efficacious orally as it is parenterally. Despite its poor affinity for opioid receptors, roughly 10% of codeine supplied undergoes O-demethylation to morphine, and the accompanying analgesic action is mostly owing to this conversion. The antitussive effects of codeine may, however, be due to codeine attaching to particular receptors for the alkaloid. Codeine is most typically used as an analgesic when taken orally, especially when combined with ASA (acetylsalicylic acid, aspirin) or acetaminophen. (18,20,21).

structure, Codeine 2 is very similar to morphine although with poor analgesic properties and moderate pain-relieving effects. Sanflippo [40] found that codeine is metabolized to morphine with simply adds a methyl group to the phenolic hydroxyl group in morphine (from an –OH to a –OCH₃). As it was already mentioned, this change results in decreasing analgesic activity of the compound. Further, it is generally believed that analgesic properties of codeine are related to its conversion into morphine [32,41,42,43]. Therefore, the analgesic effects of codeine are almost entirely attributed to morphine which makes the pharmacokinetics of codeine unpredictable [42].



Pharmacology

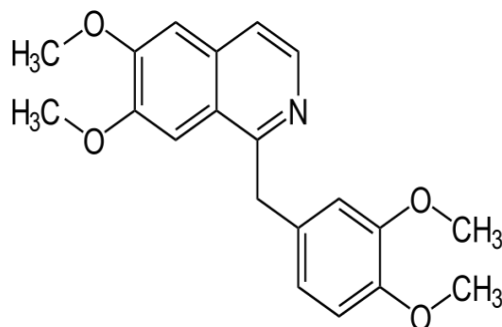
Codeine is a weak opioid that binds to the μ -opioid receptor 300 times weaker than morphine. There are three metabolic mechanisms for codeine in general. First, around 5–10% of codeine is converted to its main metabolite by O-demethylation. Second, morphine that has already been metabolized in the liver is converted to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The analgesic action of codeine is said to be linked to M6G, which has analgesic effects. The third and most important pathway involves approximately 70%–80% of codeine being directly glucuronidated to codeine-6-glucuronide 14 and 10%–15% to norcodeine 15, which is inert as an analgesic molecule. Despite the very limited conversion of codeine to morphine, there is debate on how to ascribe the analgesic benefits of codeine to morphine metabolism. [42,44,45,46]. In general, the complex metabolism of codeine and its various metabolites adds to the unpredictability of therapy with codeine [47].

PAPAVERINE

Merck isolated papaverine from opium for the first time in 1848, and it may still be isolated from opium after morphine and codeine have been extracted. In the second half of the nineteenth century, Goldschmidt and others succeeded in elucidating the structure of the alkaloid, primarily by examination of oxidation products. Pictet and Gams were the first to synthesize the alkaloid in 1909, and because the quantity of papaverine obtained from opium is so little (0.5-1.5 percent), the synthetic approach continues to be the source of this molecule to this day. Papaverine is a direct smooth muscle relaxant that works without the involvement of muscle innervation, which is especially useful when the muscle has been constricted owing to vasospasm. The smooth musculature of the bigger blood vessels, such as the coronary, peripheral, and pulmonary arteries, is relaxed. Inhibition of cyclic nucleotide phosphodiesterases is thought to be responsible for the subsequent vasodilation, which is followed by increases in intracellular levels of cyclic AMP and cyclic GMP and decreases in Ca^{++} . The alkaloid also affects the myocardium, slowing conduction and increasing irritation, as well as lengthening the refractory time. The compound's hydrochloride salt (Pavabid Plateau Caps - Hoechst Marion Roussel; Pavagen TD -Rugby) is used to treat cerebral and peripheral ischemia caused by artery spasm, as well as symptomatic alleviation of cardiac ischemia caused by arrhythmias. The alkaloid also possesses Orphan Drug status because of its use as a topical gel in sexual dysfunction in order to obtain erection in patients with spinal cord injuries (27).

Structure

Papaverine 4 is one of the alkaloids found in opium but not closely related to the other opium alkaloids in both structure and pharmacological actions. The structure of papaverine was completely identified by Goldschmidt during 1885–1898. The correctness of this structure was confirmed by papaverine synthesis [48,49]. Papaverine is a benzyloisoquinoline alkaloid produced from opium [50]. It has the molecular name 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline. Four phenolic methoxyl groups were found in Zeisel's molecule, according to Zeisel. Furthermore, degradation products revealed that methoxy groups are found in two distinct rings, each with an ortho-to-ortho configuration. In addition, an isoquinoline moiety is connected to three consecutive carbons and one outside the ring, in addition to its pyridine portion (isoquinoline). The methyl ether groups can be removed, split, or replaced, the isoquinoline N-ring can be opened or hydrogenated selectively, and the nitrogen group can be converted from tertiary to primary, secondary, or quaternary. [51, 52].



Pharmacology

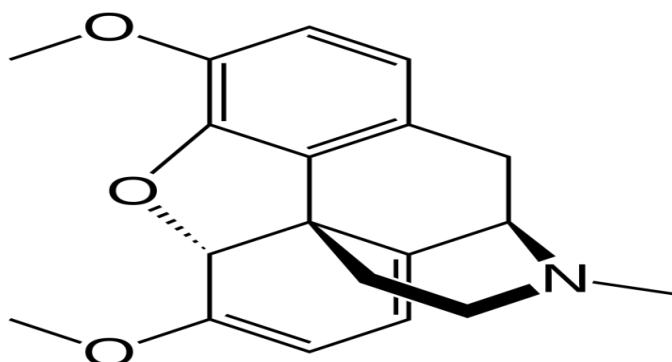
The method by which papaverine derivatives cause smooth muscle relaxation is unknown, however it appears to work outside of the cell membrane's receptor site. Some researchers believe papaverine inhibits cyclic AMP-phosphodiesterase in cells, while others believe it has a direct effect on calcium channels in smooth muscle cells. Since muscular relaxation is directly linked to a drop in cytoplasmic calcium ion levels in muscle cells, recent investigations have suggested that papaverine enhances calcium uptake via increasing cellular cyclic AMP levels. Papaverine metabolism was discovered in men, dogs, guinea pigs, rats, and cats in early research by Axelrod et al. Papaverine is almost completely O-demethylation to conjugated phenolic metabolites and metabolized principally by the liver among humans; however, it is metabolized to mono and didemethylated metabolites by demethylation among animals. In addition, some phenolic compounds including 4'-desmethylpapaverine, 7-desmethylpapaverine, 6-desmethylpapaverine, and 4',6-desmethylpapaverine were identified as metabolites of papaverine reported that papaverine and its metabolites may have a direct toxic effect on the liver; thus, the compounds need careful consideration [54,55, 61].

THEBAINE

Thebaine 3 (0.1–2.5%) is the least abundant of the hydrophenanthrene alkaloids in opium. Pelletier discovered thebaine, a minor opium alkaloid, in 1832 and named it paramorphine. Thebaine, unlike the other major opium alkaloids, has no therapeutic or medicinal value, despite its importance as a vital intermediary in the production of numerous effective opiate derivatives. Bentley and Hardy, on the other hand, were able to synthesis thebaine derivatives with substantial analgesic potencies. [69, 70]. The alkaloid is the initial opiate alkaloid and one of the primary building blocks of morphine and codeine biosynthesis in opium. At high quantities, thebaine is the most toxic opium alkaloid, causing convulsions. It is frequently utilized as an acceptable precursor for industrial semisynthetic molecules of relevant medications like as oxycodone, hydrocodone, oxymorphone, naloxone, and buprenorphine, despite the fact that it cannot be used therapeutically. [62, 63, 64, 65,71]. Moreover, thebaine is in Schedule I of the 1961 Convention due to its conversion into morphine derivatives

Structure

Thebaine 3, being the methyl enol ether of codeinone, has a molecular structure that is distinct from that of other opioids. The presence of the diene system in ring D is a unique structural property of thebaine. The molecule's overall shape, however, is comparable to that of codeine and morphine. Dienophils could target thebaine's diene system from both sides, but because of the lower steric barrier, it's more likely from the upper face of the nitrogen bridge. [69,73,74]. Therefore, thebaine is long known to take part in Diels-Alder reactions as it was reported in some studies [75,76,77].



Pharmacology thebaine is more effective at the δ -opioid receptor and its enantiomer (+)—thebaine is more effective at the μ -opioid receptor [78]. According to certain studies, there are two primary mechanisms for thebaine metabolism. Thebaine's main metabolite is pavine 16, which is metabolized by O-demethylation at the 3-position of thebaine 3. [69,79]. Oripavine binds to and receptors, and has an analgesic efficacy that is similar to morphine but substantially higher than thebaine. However, due of its considerable acute toxicity, which is significantly higher than morphine [80], it is not clinically beneficial. Thebaine, the parent component of oripavine, is probably the most useful as a possible marker of opiate consumption. [81].

MEDICINAL ASPECTS OF OPIUM

Analgesic effect

The most important medicinal effect of opium is its analgesic effect. Opioids have long been used for pain relief. Opium has been used to treat moderate to severe, acute and chronic pain. [66, 67].

Hypnotic effect

The hypnotic effect of opioids is now commonly regarded a side effect of this class of medications, thanks to the discovery of new synthetic therapies to cure insomnia. Opium and alcohol, on the other hand, are the oldest known hypnotic drugs utilized by humans. [82, 83].

Cognitive effects

Opioid abuse can lead to acute or chronic cognitive disturbance [84]

Antitussive effect

Antitussives have long been used with narcotics (such as codeine). Their antitussive effects are thought to be principally connected to the μ -opioid and κ -opioid receptors in the CNS. [85].

Respiratory depression

Opium can cause breathing problems, which can lead to death. In individuals suffering from fever associated with tuberculosis, topical opioid administration on the chest was thought to have a side effect of respiratory suppression. [68, 72].

Gastrointestinal effects

Avicenna believed opium induced constipation and prescribed it as a treatment for severe diarrhea. Recent research [85] has confirmed that opiates cause constipation. Despite the fact that opium is not usually the first choice for treating diarrhea due to its negative side effects, it is still utilized. (86).

Neuromuscular disturbances

Various theories have been proposed to explain the emergence of neuromuscular abnormalities caused by chronic opiates use. The accumulation of neuroexcitatory opioid metabolites could play a role in causing this unfavorable effect. [87].

Sexual dysfunction

Opioids can cause sexual dysfunction. This effect is part of a larger opiate-induced neuroendocrine dysfunction that leads to an imbalance in sexual hormone levels. [88].

Conclusion

Opium is the air-dried milky discharge obtained by incising the unripe capsules of *Papaver somniferum* L, according to a review of the literature (fam Papaveraceae). The cultivation of the opium poppy for the production of opium is primarily done in Madhya Pradesh in northern India. Rajasthan and Uttar Pradesh Poppy seeds are planted in late autumn or early winter in November. Morphine, Codeine, Thebaine, Papaverine, and Noscapine are the most common alkaloids found in opium. Opioids are a class of medications that are used to reduce central nervous system activity (CNS). In medical practice, the antitussive effect of other opioids such as codeine is also extensively used. The most often cited uses of poppy in ancient medicine were as a sedative and an analgesic.

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