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The Poppy Plant: Phytochemistry & Pharmacology

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ABSTRACT: *Papaver somniferum* Linn., the poppy plant, is the one of the oldest medicinal plants used worldwide. The latex obtained from the unripe capsules as exudates contains alkaloids having great analgesic properties and is called as opium. The alkaloids are biosynthesized in the laticiferous tissue of the capsule and are isolated by various chromatography techniques. HPLC and Capillary electrophoresis techniques have been used for the quantification of various alkaloids of the plant by the use of solvent system like ammonium acetate:acetonitrile, methanol:sodium acetate etc. at certain specified pH. The wide array of chemicals determined shows the possibilities and prospect for further researches. The opium has pain relieving property also inducing euphoria, hallucination and sedation and is also the most abused plant; opium pipe smoking as well as oral and intravenous use of isolated chemicals. Morphine is the major alkaloid obtained from the plant and also the most effective natural alkaloid for pain reduction, which acts on G-Protein coupled receptors (GPCRs). Codeine, thebaine, papaverine, noscapine are the other alkaloids numerically significant having decreased analgesic activity than morphine. Codeine and noscapine has antitussive activity. The pharmacological activity and phytochemistry of the plant still have many unprecedented areas which are of great interest in pharmacognostical and therapeutic research.

KEYWORDS: *Papaver somniferum*; Opium; Opioid; Opiates; Latex; Alkaloids; Benzylisoquinilone Alkaloids; Heroin; GPCRs (G-Protein Coupled Receptor).

INTRODUCTION

Medicinal plants and human civilization have lifelong relation(1) as they have been nurturing the world with the vast range of chemicals effective on various diseases and malfunctions like hypotensive drugs. analgesics, anaesthetics, anticancer and anti-parasitic compounds, anti-inflammatory drugs, steroids, laxatives, diuretics and many others(2). Natural product chemistry, an ancient science, has made it possible for the phytochemical analysis of plants which has established its potent medicinal importance of specific plant(3). Acknowledgement of these botanical knowledge by the botanists like Theophrastus(4) in Historia Plantarum , Pliny(5) in Natural history etc gave rise to traditional systems of medicines like Chinese, Ayurveda, Middle Eastern, European, African and America(6, 7). As these compilations were based on ethno medical practice, psychoactive plants had remarkable position as their use are even ritualized and religiously linked showing an early relation with humans(8-10) be it the use of sacred mushroom(11), a powerful narcotic *Cannabis sativa(12)* or a well-known hallucinogen opium poppy, which is also named as “God’s own Medicine” and “Destroyer of Grief”(13).

Papaver somniferum , commonly known as opium poppy, is an annual herb of height 50-150 cm(14) having tapering roots(15) and glaucous stem and leaves. Plant is characterized by its entire sessile leaves, dentate margin and amplexicaul cordate leaf base clasping the stem. The plant bears solitary flower borne on a slightly hairy peduncle with caudcous sepals and flowers are seen in Spring-summer season. The color of petals varies from bright as pink, red or purple to colorless (white)(16). Opium has unilocular ovary with parietal placentation bearing numerous ovules.

Taxonomically *Papaver somniferum* Linn. is a plant of family Papaveraceae which is distributed around the globe depending upon the varieties. Indian opium *P. somniferum* var. *album*, is cultivated variety of India and it bears white flower and white seeds and its capsule is somewhat egg-shaped. Similarly, next variety *glabrum* is native to Turkey(Asia minor: Myanmar, Thailand, Lao's people's Democratic Republic(17) etc.) which is recognized by its purple flower(sometime white) and purplish-black seeds, and sub-globular capsule. Similarly *nigrum* variety is a cultivated variety of Europe and it has purple flowers and slate grey seeds known as "maw seeds" and the plant is cultivated for its seeds. A wild variety of opium is *setigerum* and is identified by the bristly hairs covering peduncles and leaves along with its sharply pointed leaf lobes terminating into a bristle(14, 18). In general, the poppy plant is cultivated in warm and temperate regions of Asia, Europe and N. Africa(19).

Common names(20):

Opium poppy, common poppy, garden poppy, chessbolls,
Bale-world (English)
Kas-kas, kashkash, afin, afyun (Hindi)
Ahifen(Sanskrit)
Pasto (Bengal)
Aphina, khuskhus, posta (Gujarat)
Abini, gashagasha, kasakasa (Tamil)

Taxonomical Nomenclature(21):

Kingdom: Plantae
Sub-kingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnolopsida
Sub class: Magnoliidae
Order: Papaverales
Family: Papaveraceae
Genera: *Papaver*
Species: *P. somniferum* Linn.

HISTORY

The poppy plant is one of the oldest known medicinal plant(22) of the world. Evidence dated long ago to 4200 B.C.(23) shows poppy seeds and poppy capsules were found in the caves of Albunol, close to Geranda (Spain). Lately new evidence showing its association with human was found in the underwater La Mar-Motta site in Lake Bracciano, Italy, northwest of Rome about 35 kilometers from the Tyrrhenian Sea(24). It was Hippocrates, the father of medicine who acknowledged medicinal use of opium in 460 B.C. as styptics and analgesic(25). Similarly Linnaeus nomenclature of opium poppy as *Papaver somniferum* meaning sleep inducer(26), also focused on its activity.

It was extensively used in19th century to cure nervous aliments; depression and anxiety(13). The narcotic drug obtained from unripe seedpods of opium poppy is one of the world's oldest painkillers and human society have been practicing it as an analgesic and sedative(27).The use of opium got lesser for its medicinal property as opium became the drug of abuse to induce hallucinogens. In China, opium was a popular "cure-all" which had caused people to rely on opium for any disease though in the presence of medical treatment(28).

China had been using opium for medicinal purposes some thousands years back but the drug in itself got misinterpreted for its soothing effect(29). Despite the effort of Chinese emperors to embargoes opium consumption for smoking, famous "opium wars" of 1839 to 1842 and 1856 to 1860 with British Empire broke off giving rise to some biased agreements along with the opium cultivation shifting to China(30). This led to an ill practice of opium smoking and eating across the globe, starting from China itself. China could not control national opium consumption and production, and world suffered from the biggest addiction(27).

Also a record from New Orleans Pharmacists sampling contents dated from 1870s and 1880s, opium or morphine were containing prescription were 24.5 percentages(31). Many of these factors increased opium abuse and its illicit use, as by 19th century opium smoking trend had already started in China and the illicit use of heroin through nasal route with porcelain bowls and bamboo tubes got transcended across East Asia and United states(22). Also the cultivation of opium poppy moved to the Golden triangle hills and mountains i.e. Myanmar, Laos and Thailand(32)from China making them the present centre of Opium trade and trafficking.

OPIUM, OPIOIDS & OPIATES

Opium refers to the dried chemical latex exudates from the incision of unripe capsule of *P. somniferum* L(14, 15, 33) while the dried ripe capsules and the empty dry ripe capsule can also be used(34). Opiates in specific refers to the naturally occurring alkaloids of poppy plant while the term 'opioid' refers to all those chemical, natural or synthetic which binds to the opioid receptor and are antagonized by naloxone(35).

The raw opium obtained from incision of the capsule is either spontaneously air-dried or dried by artificial heat which is manipulated to form cakes of uniform composition but variously shaped according to the countries(36).

Manipulated Turkish opium(37)

Brick shaped masses
About 13-15 cm long
10-12cm wide
10-12cm thick

Indian opium(37)

cubical/rectangular blocks or masses
weighing 1-10 kg
wrapped in grease-proof paper/plastic material
hard and brittle to plastic consistency

Opium includes soft and shiny masses of various sizes which on drying changes to hard and brittle forming irregular shaped masses (natural opium) or some uniformly sized and shaped masses(manipulated opium) (38).

Organoleptic character:
Color: Blackish Brown
Odor: Strong characteristic
Taste: Bitter(36)

Prepared opium may differ in above specified organoleptic character as it is light brown powder consisting of yellowish brown or brownish red particles(39).

The opium latex is associated with the specialized cells called as laticifers(40)which are of two types; the articulated and non-articulated ones. The poppy plant consists of articulated type of laticifers which consists of series of cells and when cell wall breaks down, it forms laticiferous vessels(41). Nowadays, the pharmaceutical poppy alkaloids are extracted from the dried laticifer cytoplasm, dried capsules, or poppy straw(42). The young laticifer initials contains many typical cell organelles and on its differentiation, from the dilated ER a surplus number of membrane-bound vessels(43, 44) are formed which have been found to be filled with a dominating amount of phenanthrene alkaloids(45, 46). Mature laticifers contains metabolically active enzymes; both for general cellular function and biosynthesis of opium alkaloids(47).

MICROSCOPY OF OPIUM

A suspension of raw Opium, observed under a microscope, in a 20g/l solution of potassium hydroxide, appears as agglomerated latex granules in irregular masses(48). Powdered opium viewed through the system of lenses shows amorphous leaf masses, fragments of leaves and portion epicarp of the capsule, pointed trichome, brown stone cells, narrow spiral vessels or pieces of vessels, parenchyma, starch grains and refrigerant crystals(14, 18). Exhaustively washed opium with water can be used for isolation of plant debris in the sample, viewed under the microscopy(49).

The poppy capsule fragments exclusively bears 5-6 sided walls epidermis with thickened walls, outer epidermis is unlignified tubular cells (20-50µ in either direction with moderately thick anticlinal walls). And sometimes with anomocytic stomata (also in section view) which are about 17µ wide and 25µ long or sometimes circular with 20µ diameter(39, 49, 50).

But powdered poppy capsule is recognized by inner subrectangular or slightly sinous celled (85-245µ long and 18-50µ wide) epidermis of pericarp with lignified and pitted anticlinal walls, about 7cm thick. Also an adequate number of stomata, 25-35 µ in diameter can be observed.

Occasionally some sub spherical three pored structures may be observed which have a probable dimension of 16 to 20 – 30 to 40 µ in diameter. Rarely, pieces of upper and lower epidermis of foliage leaves with thin polyhedral cells bearing anomocytic stomata only on the lower epidermis may also be seen. Very few quantity (almost absent) of starch grains may be distributed which are of 4-8µ in diameter(39).

CHEMICAL CONSTITUENTS

Alkaloids are the chemical of interest in opium. Besides it also consists of a complex mixture of proteins, sugars, fat, resin, coloring substances, wax, rubber, salts (e.g. sulphates), albuminous matter, water and mucilaginous substances. Opium alkaloids re combined with number of simple organic acids including fumaric acid, lactic acid, and the rare meconic acids(14, 51).

S.N	Chemicals	Percentage composition
1.	Alkaloids	10-20
2.	Sugars	20
3.	Water	5-20
4.	Meconic acid	3-5

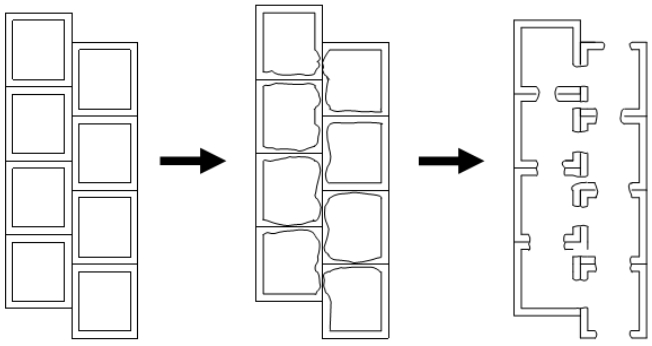


Figure 1 1-Articulated laticifers of Opium poppy; 2- Porous cell wall formation due to thinning; 3- cells are connected forming latex vessels.

Meconic acid, either in ionized form as meconate or in unionized form, is present in genus *Papaver* (also in some closely related genera such as *Meconopics* and *Roemaria*) hence is used as chemotaxonomic marker. Its presence can be located by a chemical test through red color detection with 10 % ferric chloride solution which remains unaltered with addition of dilute hydrochloric acid(52).

Similarly, a trace alkaloid, Porphyrixine, is also used for chemical analysis of opium as it produces intense red color with when sample emulsion with one drop of water is transferred to a spot plate containing mineral acid (2N Hydrochloric acid)(49).

Alkaloids of opium can be classified broadly into two major classes(26):

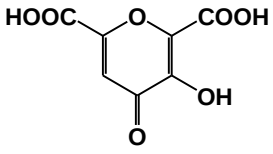
a) The benzoisoquinoline alkaloids

These groups of compound have benzoisoquinoline nucleus e.g. Papaverine, Noscapine etc.

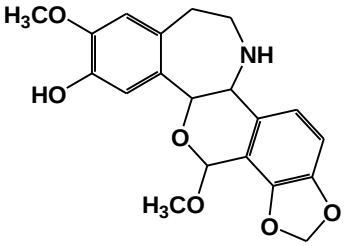
b) The phenanthrene alkaloids(Morphinane alkaloids)

This alkaloidal class is recognized with its phenanthrene nucleus. E.g. Morphine, Codeine, Thebaine etc.

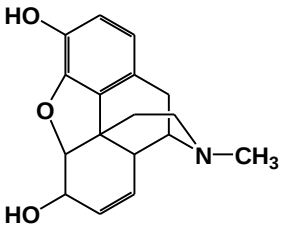
Among all alkaloids morphine is the major and opium is tested for its content which should be not less than 9.5%(36), while other alkaloids are found with variable content ratio. Codeine content is generally between 0.3-4%, highest of it being in the Indian opium(37). In a study by Shukla et al, opium latex of 140 plant samples within 98 germplasm lines, morphine was the major constituent followed by noscapine, codeine, thebaine and papaverine(53). While the rest alkaloidal concentration was found different by Dittbrenner et al, variability was seen with concentration of noscapine, papaverine or codeine following morphine(54).



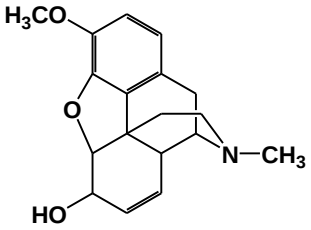
Meconic acid



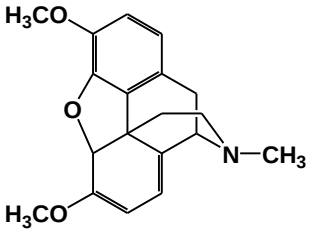
Porphyroxine



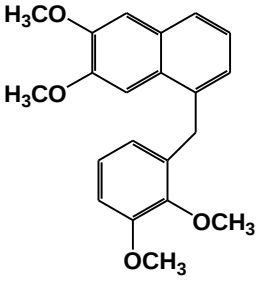
Morphine



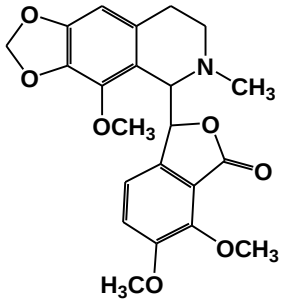
Codeine



Thebaine



Papaverine



Noscapine

Besides these major 5 alkaloids, many other alkaloids (2.5-6%) are also isolated from *Papaver somniferum.* Sanguinarine, Salutarifine, Narceine, meconidine, codmine, laudanine, laudanosine, neoprene, lanthothine, protoprine, cytopine, oxy-narcoteine, gnoscopine, xanthaline(papaveraldine), rophyroxine, narcotisline, papaveramine and possibly others occurring partly in free state and partly in combined state with meconic acid and sulphuric acids(37).

QUANTIFICATION, DETERMINATION & SEPARATION OF OPIUM ALKALOIDS

The extraction of opium alkaloids from dried opium sample is carried using aqueous acetic acid as a solvent(55). The dried sample, 1 gm, is dissolved in 2.5% aqueous acetic acid and shaken mechanically for 30 minutes. After centrifugation at 5000 rpm the supernatant layer is decanted off and filtered using G3 sintered filter. The extraction process is repeated thrice and the extract is made 100 ml with addition of 2.5% aqueous acetic acid(56).

Opium alkaloids quantification can be done by one of the many methods; High Performance Liquid Chromatography HPLC(57, 58), Gas Chromatography GC(59), Gas-Liquid Chromatography(60), Capillary electrophoresis(56, 61), Paper chromatography(62), and Thin layer chromatography(48).among these capillary electrophoresis, GC, HPLC and Gas-liquid chromatography are more desirable ones as they are modern techniques and less tedious than older ones. Capillary electrophoresis technique has eradicated problem associated with HPLC to separate alkaloids of almost similar polarity like that of morphine and codeine, still HPLC is more frequently used and preferred over GC. In HPLC method separation and detection of major opium alkaloids is best performed by reversed phase HPLC on porous stationary phases. When analyzed for analysis time of 20 minute, a specific determination of morphine, codeine, thebaine, papaverine and noscapine alkaloids as major alkaloids of opium was seen. Mobile phase used for the method was 0.1% of aqueous heptafluorobutyricacid with 60:40 acetonitrile-water containing 0.8% heptafluorobutyric acid(58).

Alkaloids	Retention time
Morphine	0.30
Codeine	0.43
Thebaine	0.66
Papaverine	1.04
Noscapine	1.31
T_0	0.23

Table 1:- Gradient elution Reversed Phase DPLC retention of the major opium alkaloids

Also capillary electrophoresis technique employed by unger et al separates major opium alkaloids as thebaine, codeine, morphine, papaverine and narcotine (noscapine), detected by ultraviolet light at 224nm; acetonitrile-water 1:1 as running buffer with ammonium acetate 100mM at 3.1. The coupling of mass spectroscopy with capillary electrophoresis in the process also showed the fastest movement of thebaine followed by codeine and morphine due to more lipophilic character of thebaine attributed by methyl group over hydroxyl group(63). While it's observed that replacement of acetonitrile by methanol and ammonium acetate with sodium acetate as run buffer 3:7, 100mM of sodium acetate at 3.1 pH for optimum separation of alkaloids peaks; the optimum voltage for both the experiment being 15kV. The percentage concentrations in gram percentage as observed by capillary zone electrophoresis in five crude samples of gum opium by Reddy et al was in the range of 14.45-15.95(morphine), 2.0-3.5(codeine), 1.32-2.73(thebaine), 0.92-2.37(papaverine) and 3.85-5.77(narcotine)(56).

While various chemical tests(49, 50, 64) have been designed for careful determination of these chemicals, which is necessary for the analysis of the quality of opium. As mentioned above, meconic acid test and test for porphyrine also involves opium identification test. Other test involves tests of opiates like morphine, codeine etc. e.g. marquis test which gives purple violet color with morphine and codeine, bright yellow color with noscapine, while the papaverine gives no coloration. Similar to Marquis are Mecke and Frohde tests which has been used by United Nations for qualitative analysis of opium and for the management of smuggling of the drug.

Anions tests are also performed which involves tests for chloride, sulphate, citrate, tartarate ions where chloride, citrate and tartarate produces white precipitate with silver nitrate and barium chloride is used for sulphate precipitation.

BIOSYNTHESIS OF OPIUM ALKALOIDS

The alkaloids biosynthetic enzymes have been isolated from to the parietal region of sieve elements adjacent or proximal to laticifers(52, 65) when immunofluorescence labeling using affinity-purified antibodies was performed; three key enzymes involved being, (*S*)-*N*-methylcoclaurine 3-hydroxylase (CYP80B1), berberine bridge enzyme (BBE), and codeinone reductase (COR), involved in the biosynthesis of morphine and the related antimicrobial alkaloid sanguinarine.

L-tyrosine is the precursor amino acid precursor for these opium alkaloids. Oxidative deamination of L-tyrosine followed by decarboxylation gives 4-hydroxyphenylacetaldehyde, which is an essential chemical for the biogenesis of these alkaloids. Besides, L-tyrosine on decarboxylation also gives tyranine which is subsequently oxidized to dopamine. The chemical reaction for the synthesis of these alkaloids starts with the condensation o f dopamine and 4-hydroxyphenylacetaldehyde(66) by norcoclaurine synthase enzyme producing (S)-norcoclaurine , whereas norcoclaurine 6-O-methyltransferase (6OMT) and coclaurineN-methyltransferase (CNMT) convert (S)-norcoclaurine to (S)-N-methylcoclaurinewhich converts to (S)-coclaurine on methylation of the former. (S)-cocularine

serves as the turning point for the production of benzyl isoquinoline alkaloid papaverine, the phthalideisoquinoline alkaloid noscapine, and morphinans morphine, codeine and thebaine. (S)-Cocularine gives (S)-Reticuline which on epimerization yields (R)-Reticuline molecule, which is the key precursor for morphinaian alkaloids production. The NADH-dependant enzyme codeinone reductase (COR) converts (-)-codeinone to (-)-codeine as the penultimate step in morphine biosynthesis.

USES

The plant is used for its analgesic alkaloids while its seed has use in nutraceuticals or culinary as it contains oils which can be used for various properties. The opium plant bears variously colored flowers and is planted also for its beauty. Poppy seed oil has been as a culinary salad oil**,** cooking oil, drying oil for use in art, and as a vehicle for various parenteral formulations.(67, 68)

Pharmacologically opium has analgesic and narcotic action mainly due to its major alkaloid content as morphine followed by codeine and thebaine. Freidrich Wilhelm Adam Serturner isolated Morphine form opium poppy and named as "Morpheus" meaning Greek god of dreams due to its pain relieving property(69). Opium is less potent than pure morphine in its analgesic property as it occurs in mixture of various chemicals and has hypnotic activity(14). Opium alkaloids act on sensory nerve cells of the cerebrum and show its effects.

Morphine shows its activity by mimicking naturally occurring opioid peptides i.e. endogenous opioid peptides such as enkephalins, endorphins and dynorphins, as it is a full agonist at μ receptor in CNS(70). These alkaloids or the opiates mediate their pharmacological effect by four families of receptors designated as μ, δ, σ and κ(71), a class of G-Protein coupled receptors(72, 73).

The opioid signaling chain in the body is operated through G protiens by acting on several targets such as enzyme system, ion channel etc. the receptors undergo conformational change as morphine binds to it and causes expulsion of GDP molecule and attachment of GTP molecule to the G protein. The activated G protein breaks into two; one with GTP diffuses across the membrane and act on specific target molecules. They either binds to adenyl cyclase and inhibits the formation of cyclic AMP or act on potassium channel increasing the K^+ conduction or on calcium channel decreasing Ca^+ conduction leading to decreased transmission of pain stimulus(74). Also receptor activity through second messenger system like activation of MAP kinases and phospholipase C forming inositol triphosphate and diacylglycerols have been shown by some studies(70).

Most of the opioids induce analgesia, euphoria, sedation, and respiratory depression and lead to high degree of tolerance to all these on repeated use of opioids. The adaptation of receptor to prolonged exposure of opioids results in tolerance, sensitization and withdrawl(72). Morphine action on GIT has been used for diarrhea as it reduce GIT motility(75). Codeine is milder analgesic than morphine and is useful for allaying cough.

Papaverine relaxes smooth muscle without paralyzing it and is effective in hypertension as it is found to produce a marked vasodilation, also used in angina pectoris and abortion of uremic crisis(76). Noscapine, the other isoquinoline alkaloid is an antitussive agent(77) and besides other is an antineoplastic or anti-mitotic agent(78); inhibit the growth of tumor cells by targeting tubulin leading to abnormal assemblage of mitotic spindle(79).

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