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The Review of Power of Poppy: Harnessing Benefits of Nature's Most Dangerous Plant

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Abstract

Morphine is an alkaloid isolated from opium poppy (*Papaver Somniferum* L.) and known to have number of structurally related alkaloids such as (-)-codeine and (-)-thebaine. It has a strained pentacyclic core with five contiguous chiral centers including a benzylic quaternary carbon. Naturally morphine can be obtained from poppy plant however various synthetic routes make its availability easier for number of medicinal formulations and pharmaceutical applications. Morphine can be synthesized biochemically in mammalian cell and through endogenous de novo synthesis while some chemical methods include Gates, Rice, Parker, Fukuyama, Hudlicky, Iorga and Guillou, Chida, Magnus and Stork synthesis. Morphine and its derivatives can potentially be characterized by LC-MS-MS, crystallography, HPLC with ultraviolet spectrophotometer, ATR-FTIR, FT-Raman spectroscopy, voltammetric sensor based detection, amperometric detection and surface plasmon resonance based immunosensor, chemiluminiscence detection with HPLC, HPLC with fluorescence detection and by graphene nano-sheets modified by glassy carbon electrode. Morphine is used as analgesic for both acute and chronic pains. Morphine is frequently used for pains relief arising from myocardial infarction, labour pains, acute pulmonary oedema, lung cancer, breast cancer, prostate cancer, prostate bone metastasis in rats, severe pain in bones and intense pain in joints, sickle cell anemia, pain of kidney stones, rheumatoid arthritis and osteoarthritis. Some potential bioactivities shown by morphine and other compounds of opium include hypnotic and analgesic effects and anti-microbial and anti-parasitic activities.

Key words: Morphine, codeine, thebaine, myocardial infarction, pulmonary oedema, lung cancer, rheumatoid arthritis, osteoarthritis, hypnotic effects, anti-microbial activities

Full length article **Corresponding Author*, e-mail: farwa668@gmail.com

1. Introduction

Poppy (*Papaver somniferum* L.) is dicotyledonous plant that is cultivated for opium, oil and seed and belongs to family Papaveraceae. It is an annual erect herb that can attain the height of 30 to 170 cm having ovate flower buds with dropping before anthesis. Its fruit is a capsule constituting large number of smaller seeds. Some cultivars are also known to contain more than 50% fatty oil in its seeds in form of linoleic acid and oleic acid as major components. This oil is of very high quality for human consumption as it contains appreciable concentration of valuable polyunsaturated fatty acids [1]. In English, it is called "poppy seeds", in Tamil it is called "kasakassa", in Malayalam it is called "kaskas" and "kashakasha", in Telugu it is called "gasagasaalu" and "kasakasa", in Kannada it is called "gasagase beeja" and "kasa kase", in Hindi it is called "post dana", "khuskhus" and "kashash", in Bengali it is called "posto", "kashash" and "afing", in Gujarati it is called "khaskhas", "khuskhush" and "aphim", in Konkani it is called "khus-khus" and "koskoso", in Marathi it is called "khaskhas" and "khus khus", in Oriya it is called "posta" and "aphima", in Punjabi it is called "khus khus", "khas" and "post", in Tulu it is called "gasa-gase", in Urdu it is called "kashkash sufaid" [2].

Poppy seeds are produced inside the annually growing colorful flowers that are famous in Middle East, India and Europe due to having nutty flavor and extreme crunch. Slate blue seeds of poppy flowers are favored by Europeans more specifically for cooking and baking food article such as breads, bagels, muffins and pastries. Dry roasting or toasting is commonly practiced in order to ensure the best flavor of seeds. Poppy plant can attain the height of 5 feet but require highly fertile soil and full sunshine for proper growth and development. Based on the type and variety, poppy plant can be having white, red, blue or lilac flowers during spring season on the top of long peduncles that subsequently turns into oval or globular shaped fruit. Saponification value, acid value, fatty acid profile and

essential oil contents of poppy seeds have extensively been studied in number of scientific investigations and collected evidences have shown that seed oil majorly constitutes opium alkaloids including codeine and morphine along with vitamin-E and some essential fatty acids such as palmitic acid, oleic acid and linoleic acid. Poppy seeds are known to contain approximately 44 to 50% fixed oil having oleic acid and linoleic acid [3]. By statistical analysis, it has been analyzed that there is a significant effect of genotype, locality and their interactions for numerous descriptors that were proved to be non-parametric tests [4].

Morphine is a well-known principal alkaloid isolated from opium poppy (*Papaver Somniferum* L.) and a number of structurally related alkaloids like (-)-codeine and (-)-thebaine that have also been discovered in the same plant. Its important biological activity as well as highly challenging structure (strained pentacyclic core with five contiguous chiral centers including a benzylic quaternary carbon) has naturally received considerable attention from the synthetic community [5]. Morphine is a benzylisoquinoline alkaloid with two additional ring closures. It has a rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a tetrahydrofuran ring (E) as shown in figure 1. Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility. Two hydroxyl functional groups C3-phenolic OH (pKa 9.9) and a C6-allylic OH, an ether linkage between C4 and C5, unsaturation between C7 and C8, a basic tertiary amine function at position 17, 5 centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action [6]. Morphine has a pentacyclic structure with a benzylisoquinoline nucleus supporting ether, hydroxyl and olefinic functions [7].

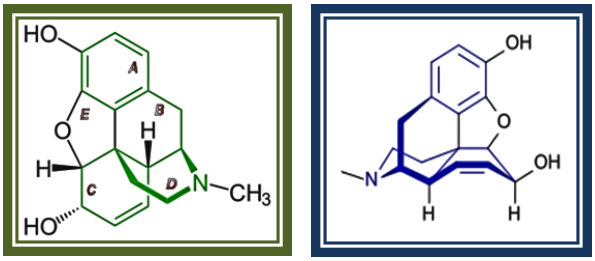

Fig 1 Structure of Morphine

Traditionally, drugs were obtained through extraction from medicinal plants but more recently also by organic synthesis. Pharmaceutical drugs may be used for a limited duration or on a regular basis for chronic disorders mainly [8]. Biosynthesis of morphine in mammalian cell and endogenous production of morphine by de novo synthesis has recently been reported. Methods of chemical synthesis of morphine include Gates synthesis [9], Rice synthesis [10] and Parker synthesis [11] were methods of early synthesis of morphine. Recently, Fukuyama synthesis [12], Hudlicky synthesis [13], Iorga and Guillou synthesis [14], Chida synthesis [5], Magnus synthesis [15], Stork synthesis [16] and improved Fukuyama synthesis [17] are the most common routes of production of morphine by chemical synthesis.

Characterization of morphine and its derivatives is made possible by different analytical techniques such as LC-MS-MS [18], crystallographic detection [19], HPLC with ultraviolet spectrophotometer [20], ATR-FT-IR, FT-Raman spectroscopy [21] and voltammetric sensor based detection [22]. Amperometric detection [23], surface plasmon resonance based immuno-sensor [24], chemiluminiscence detection along with HPLC [25], HPLC with fluorescence detection [26] and by graphene nano-sheets modified glassy carbon electrode [27] are also important methods of detection and characterization of morphine.

Morphine is a pain medication of the opiate type. It acts directly on the central nervous system (CNS) to decrease the feeling of pain thus used as analgesic. It can be used for both acute pain and chronic pains. Morphine is also frequently used for pain from myocardial infarction [28] and during labour [29]. It can be used for the acute pulmonary oedema [30], lung cancer, breast cancer pain, prostate cancer pain [31], prostate bone metastasis in rats [31], severe pain in bones and joints, sickle cell, pain due to kidney stones, rheumatoid arthritis and osteoarthritis. It is also used as general anesthesia to sedate a patient [29]. Some common side effects include drowsiness, vomiting, low blood pressure and constipation. Caution is advised when used during pregnancy or breast feeding as morphine will affect infant. Morphine was reported to increase the proliferation of endothelial and tumor cells [32]. On the other hand, morphine and other opioids were also found to promote tumor cell death [7]. The perfect accurate dose of morphine according to disease and patient's body conditions is essential [33].

2. History

Morphine is one of the oldest drugs known to mankind. Sir William Osler, a Canadian physician, called morphine "God's Own Medicine", advocating the use of natural substances in medical applications. Before and after Serturner's isolation of the active ingredient of opium in 1806, writers commemorated its effects. It took 125 years from its isolation by Serturner for the structure of morphine to be solved and two more decades before Gates reported the first total synthesis. After Gates's synthesis and during the golden era of total synthesis of natural products, many other syntheses methods of morphine alkaloids were also followed [34]. Opium is an extract of exudate derived from seed pods of the opium poppy (*Papaver somniferum* L.). The poppy plant was cultivated in the ancient civilizations of Persia, Egypt and Mesopotamia. Archaeological evidences and fossilized records of poppy seeds suggested that Neanderthal man may have used the opium poppy over thirty thousand years ago. Less controversially, the first known written reference to the poppy appears in a Sumerian

text dated around 4,000 B.C. The flowers of poppy were previously known as "Hul Gil", the plant of joy.

Fig 2 Opium Poppy

Physicians commonly believed that the poppy plant was of divine origin, opium was previously called as "sacred anchor of life", "milk of paradise", "hand of God" and "destroyer of grief". Thomas Sydenham writes: "among all the remedies which it has pleased almighty God to give man to relieve his suffering; none is as universal and efficacious as opium".

3. Natural Occurrence

Opium is a naturally occurring drug that is cultivated directly from the poppy plant (*Papaver somniferum* L.). Poppy plants typically grow upto a height of 3 or 4 feet. On top of the stalk, there is a large globe like bulb that contains the seeds of the poppy plant. Surrounding the bulb are the petals of the poppy flower. Although the flowers vary based on species and growing conditions, the opium producing poppy plant is usually marked by the presence of red or purple flowers and a bulb that contains yellow seeds.

Fig 3 Purple and red flower with yellow seed

As the poppy plant ripens, the flowers that surround the poppy plant's pod fall off, exposing the bulb. Once this occurs, there is a noticeable drooping in the stalk of the plant. As a result of this process, the opium sap that resides within the pods will ooze out at the site of the incisions and adhere to the pod. During next twelve hours, sap turns brown as it interacts with the air [35].

Fig 4 Milky white and brown sap of opium poppy [35]

4. Ideal Location

This plant is found native to Middle East but also found to grow in Afghanistan, India, Indo-China and China. Some of its varieties also grow in extreme wild areas of North America and Europe. This plant is indigenous to Middle East but also widely grown in Turkey, Russia, Romania, Poland, Iran, Holland and Argentina. Poppy seeds require full sunshine and thrive in dry and relatively warm climate. Poppy is also grown in some remote areas and mountain ranges of Tak and Nan Provinces, Mae Hong Son, Chiang Rai and Chiang Mai in Northern Thailand. It can grow in almost all types of soils ranging from dry and finely textured soil to friable soil type. The optimum growth can be evident in sandy clay, sandy loam and soil clays however maximum yield can be obtained in sandy loam soil as it is full of nutrients and have maximum moisture retention capacity. It can be easily cultivated with extensive root system development. Some major poppy growing legal areas include ingovernment regulated opium farms of Australia, Tasmania, Turkey and India. Globally elicited cultivated areas of opium were estimated to be about 189,000 hectors in the year 2008 mainly located in Afghanistan followed by Lao PDR and Myanmar. Global production of opium was estimated to be 8000 tons in the year 2008 [36]. Its annual production in Czech Republic is 49248 metric tons, in Turkey 10384 metric tons, in France 5000 metric tons, in Hungary 3300 metric tons and in Germany 2800 metric tons [37].

5. Derivatives of Morphine

Poppy (*Papaver somniferum* L.) is a 2 to 3 feet tall hardy annual plant that is specifically grown for its seeds that are used for culinary purposes. Poppy is an erect plant attaining 60-120 cm height. It is rarely branched. The leaves are oblong or ovate having a dentate and serrate margin [38]. Morphine is the major chemical constituent of this plant that has large number of structurally related derivatives extensively used for various fruitful applications. Morphine and its derivatives continue to attract the undiminished attention of organic chemists all around the globe. Two commercially produced derivatives are naltrexone and naloxone that are used for treatment of opiate overdoses and alcohol addiction. These are related to noroxymorphone which is manufactured from morphine or thebaine [39]. Some typical examples are shown in figure 5.

6. Chemical and Biochemical Synthesis of Morphine

Morphine is a naturally occuring highly valuable chemical constituent of opium plant that is most commonly used in medicinal formulations and pharmaceutical drugs for number of fruitful purposes and useful applications. However, inspite of large scale cultivation, tremendous legislative hurdles still exist in its worldwide production. Therefore, scientists more specifically organic chemists have struggled hard in order to find out its synthetic routes through various chemical and biochemical processes. In past few decades, morphine has been evident to be synthesized biochemically in mammalian cell and via endogenous de

novo synthesis while some chemical methods include Gates synthesis, Rice synthesis, Parker synthesis, Fukuyama and improved Fukuyama synthesis, Hudlicky synthesis, Iorga and Guillou synthesis, Chida synthesis, Magnus synthesis and Stork synthesis.

7. Chemistry Composition

Poppy (*Papaver somniferum* L.) is a well-known medicinal plant that is widely cultivated and abundantly used for various pharmaceutical products all around the globe owing to unique chemical composition of different parts of this plant. Poppy seeds are a rich source of vitamin E and several other tocopherols including γ-tocopherols and α-tocopherols along with phytosterols and sterols such as Δ-5-avenasterol, sitosterol, stigmasterol and campesterol. Some essential fatty acids in the seeds of poppy plant include linoleic acid, oleic acid and palmitic acid. Specific aroma and unique flavor of this plant is mainly attributed to the presence of 2-pentylfuran, 1-hexanal, caproic acid, 1-hexanol and 1-pentanol [40]. Phytochemical analysis of this plant has evident the presence of mixture of mucilagenous substances, water molecules, albuminous matter, sulphate based salts, rubber, waxes, coloring material, resins, fats, sugars and protein molecules. Opium alkaloids are usually found in association with number of organic acids such as meconic acid, lactic acid and fumaric acid.

8. Mode of Action on Central Nervous System

Morphine produces its effect by altering the communication between neurons. A neuron's ability to communicate is partly a product of its structure and its function. Neurons like all cells have a cell body that contains a nucleus. Unlike other cells, however neurons have tubular branch like protrusions that emanate from the cell body called "dendrites" and "axons". The dendrites are mostly responsible for receiving signals from other neurons. The ability of dendrites to detect these incoming signals results from the fact that they have specialized proteins called "receptors" positioned all along their length. Like dendrites, axons are also branch like protrusions that originate from the cell body. These structures however are chiefly responsible for sending signals to other neurons.

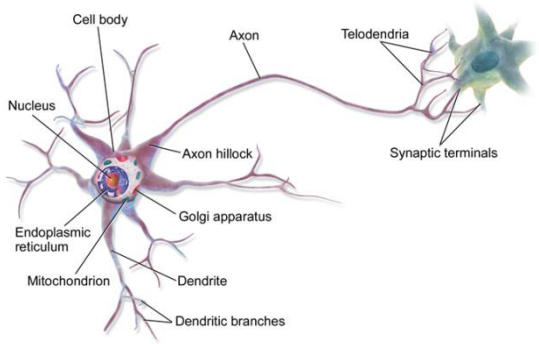

Fig 6 Structure of neuron

When a neuron's dendritic receptor receives a signal from another neuron or detects stimuli from the external environment, electrical charges enter the cell body. This internal electrical charge, now called an "action potential" which is then sent streaming down the axon away from the cell body. When this action potential reaches the end of the axon (the terminal), it triggers the release of a chemical, a neurotransmitter into the synaptic space. Given the close proximity of one neuron's axon and another neuron's dendrites, the neurotransmitter molecules are able to travel across the synapse and attach to the neighboring neuron's dendritic receptors. Then, the electrical and chemical process starts all over again, allowing the signals to continue.

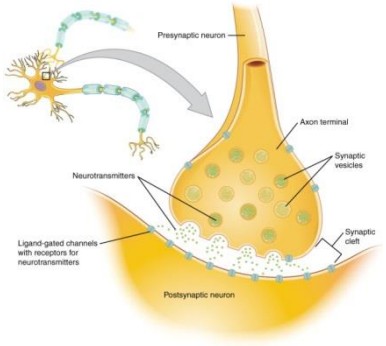

Fig 7 Post synaptic membrane of neuron

Morphine affects neurons that have certain types of receptors on them called "opioid receptors". The opioid system does not work in isolation of other neurons but rather in concert with other neuronal systems. Once opioid receptors are activated these neurons release neurotransmitters that shut down the ability of other neurons to talk with one another thereby inhibiting neuronal communication. The net result of this activity can be the alteration in sensation and perception of pain, as well as the development and maintenance of addictive behaviors morphine's ability to affect this system is due to the fact that morphine on a molecular level can act in the same manner as some of the natural neurotransmitters involved in opioid neuronal communication.

9. General Uses and Pharmacological Applications

Poppy seeds are nutritionally dense with high levels of essential minerals like calcium, iron, magnesium, phosphorus and potassium. Whole poppy seeds are used as spices of food and as decoration items. Paste of poppy seeds is used as a moisturizer. Poppy seed oil has multiple culinary, industrial and medicinal uses. Iodized poppy seed oil has an especially high rate of uptake into cells of hepatocellular carcinoma (HCC). This property was recognized and treated in case of chemotherapy and used for preparation of emulsions, in preparation of paints, varnishes and soaps. It is used in the treatment of diarrhea, dysentery and scalds [41]. The seeds of poppy plant are known to contain magnesium, zinc, manganese, potassium, calcium, copper and iron where copper promotes the production of red blood cells, zinc acts as cofactor for large number of enzymes that regulates the growth and development of new cells along with the synthesis of essential biological macromolecules, potassium helps to control the blood pressure and heart beat while manganese is an important

cofactor for number of antioxidant enzymes such as superoxide dismutase [42].

9.1 Pharmacological Uses

Opium is the plant that is known to have high medicinal value and excellent therapeutic potentials because of number of bioactive compounds and excellent bioactivities including analgesic effects, hypnotic potentials and significant influences on central nervous system. This plant is also a good source of anti-microbial and anti-parasitic compounds.

9.1.1 Analgesic Effect

The execution of analgesic effects is one of the most important medicinal applications of opium plant. Opioids have conventionally been used to relieve pains starting from severe acute pains to intense chronic pains. Analgesic effects of this plant have extensively been studied as single therapeutic agent and as essential component of number of mixed herbs for treatment of severe conditions ranging from simple headache, toothache, nostalgia and arthralgia to severe labor pains, bladder infections and kidney disorders. Opioids drugs prevents the conduction of painful nerve impulses owing to their cooling effects [43].

9.1.2 Hypnotic Effect

The hypnotic effects of opioids are now being considered as its major side effect owing to the development of various potential synthetic drugs in order to treat insomnia. Nevertheless, alcohol and opium are the best known hypnotic agents extensively used by human beings since long period of time as effective remedy [44].

9.1.3 Effect on Nervous System

Seeds of poppy protected reperfusion in rats and cerebral ischemia in hippocampus however it did not significantly alter the frequency of cell death. Administration of the extracts of different parts of poppy plant reduced the expression and acquisition of morphine induced behavioral sensitization in mouse. Furthermore, it also significantly reduced the acquisition of morphine induced conditioned place preference but not the expression. The extract of this plant can also ameliorate withdrawal syndrome in morphine dependent mouse.

9.1.4 Anti-Microbial and Anti-Parasitic Activities

Hydro-alcoholic, ethanolic and aqueous extracts of *Papaver somniferum* L. were tested against two potential acne causing bacteria *Staphylococcus epidermidis* and *propionibacterium* acnes that were proved to be catastrophic in nature.

10. Summary

Poppy (*Papaver somniferum* L.) is an important member of family Papaveraceae and found native to South East of Asia and Europe. This plant has no known wild specie but has largely been cultivated all across the globe. It is mostly grown as ornamental flower in Asia, South America, North America and Europe. Up till now, forty different types of alkaloids have been identified in this specie among which noscapine, thebaine, codeine and morphine are at the top. Alkaloids are the major constituents that are affected by environmental variations and genitival characteristics. Seeds of poppy plant are important source of many useful components that are known to have analgesic potentials and pain relieving effects. Use of poppy in medicine has long been known in traditional and ayurvedic system of medicines in India. Dried latex from poppy capsule has major therapeutic effects on severe pains, spasms, diarrhea and dysentery. However, purification of opium has vividly been described in order to balance the enhanced Pitta Dosha, Doshas, Kapha and Vata. Although it is well known that poppy plant contains analgesic such as morphine, thebaine and codeine, thebaine as well as other therapeutic constituents like sanguinarine and papaverine alkaloids yet poppy seeds do not contain opium but are coated by it. The concentration of this coating varies, depending on the amount of rainfall during the curing of the seed pods and washing of the seeds. Poppy seeds are commercially used as a topping or ingredient in baked items such as bagels, muffins and pastries and in making seed bars, candy bars or nutritional bars.

Table 1 Historical milestones in chemistry of morphine [34]

3400 BCE	Cultivation of poppies by Sumerians in Mesopotamia (Tigris−Euphrates)
2000	Use in the Mediterranean region, Europe and North Africa
1550	Use in Egypt; first written record (Ebers Papyrus)
700	Use by the Assyrians (Babylon)
700	Homer’s Odyssey (nepenthe, the drug of forgetfulness, was an opium preparation)
77 CE	Dioscorides (Greece) described method for obtaining opium from poppies
150	Galen (Rome) recommended "Mithridate", an opium concoction to patients
183	Hannibal’s suicide with opium
900	Arab texts on "af-yum" (ufian, asium)
1525	Paracelsus invents laudanum
1700	Mysteries of Opium Reveal’d Dr. John Jones
1790−1840	Use by Coleridge, Shelley, De Quincey and Crabbe
1806	Isolation of morphine (Serturner)
1828	Beginning of "Organic Chemistry": synthesis of urea (Wöhler)

1831	Empirical formula for morphine established (Liebig)
1833	Isolation of codeine (Robiquet)
1839−1842	First Opium War (China and Great Britain)
1842	Correct empirical formula for codeine established (Gerhardt)
1847	Correct empirical formula for morphine established (Laurent)
1874	Synthesis of heroin (Wright)
1881	Isolation of phenanthrene after pyrolysis of morphine (von Gerichten)
1906	Attachment of N-ethylamino bridge (Knorr)
1925	Attachment of C-terminus (Robinson)
1927	Structure proof of morphine (Robinson, Gulland and Schopf)
1952	Total synthesis of morphine (Gates)
1954	X-ray structure and absolute stereochemistry of morphine (Mackay and Hodgkin)
1980	First practical synthesis of morphine (Rice)
1985	Morphine identified in mammalian cells
2004	Development of mutant poppies (top1) producing thebaine and oripavine
2005	Morphine biosynthesis in mammalian cells confirmed
2011	Patent issued for production of thebaine and oripavine in poppies
2012	Global production: Morphine 440 t, Codeine 381 t, Thebaine 145 t and Oripavine, 23 t
2014	Low titer production of morphine alkaloids in yeast reported

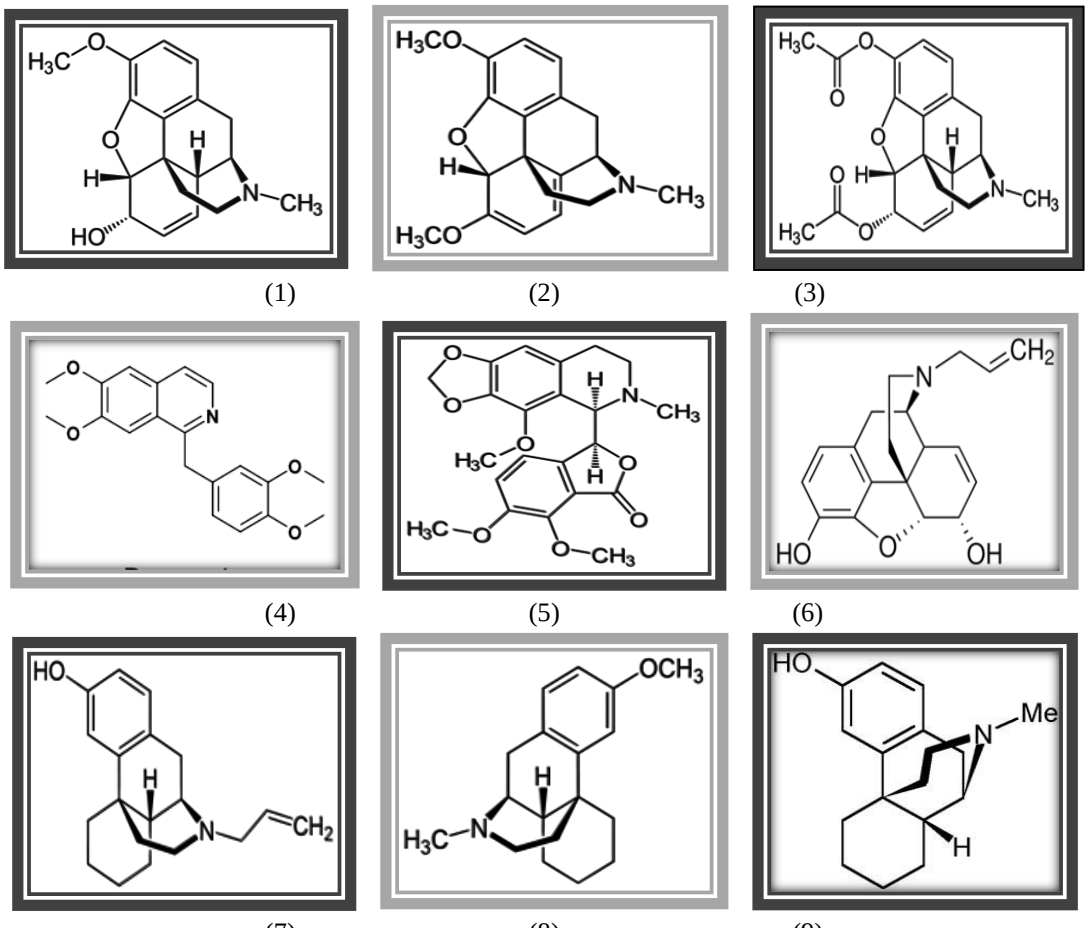

Fig 5 Derivatives of Morphine (1) Codeine (2) Thebaine (3) Heroin (4) Papavarine (5) Noscapine (6) Nalorphine (7) Levellorphan (8) Dextromethorphan (9) Levorphanol [39]

Table 2 Syntheses of morphine and its drug derivatives [34]

Author	Year	Target Molecule	Steps	% Yield
Gates	1952	Morphine	31	0.06

Ginsburg	1954	rac-Dihydrothebainone	21	8.9
Grewe	1967	rac-Dihydrothebainone	9	0.81
Rice	1980	Dihydrothebainone	14	29.7
Evans	1982	rac-O-Me-thebainone A	12	16.7
White	1983	Codeine	8	1.8
Rapoport	1983	rac-Codeine	26	1.2
Fuchs	1987	rac-Codeine	23	1.3
Tius	1992	rac-Thebainone-A	24	1.1
Parker	1992	rac-Dihydrocodeinone	11	11.1
Overman	1993	Dihydrocodeinone	14	1.9
Mulzer	1996	Dihydrocodeinone	15	9.1
Parsons	1996	Morphine	5	1.8
White	1997	ent-Morphine	28	3.0
Mulzer	1997	Dihydrocodeinone	18	5.7
Ogasawara	2001	Dihydrocodeinone ethylene ketal	21	1.5
Taber	2002	Morphine	27	0.51
Trost	2002	Codeine	15	6.8
Fukuyama	2006	rac-Morphine	25	6.7
Hudlicky	2007	ent-Codeine	15	0.23
Iorga/Guillou	2008	rac-Codeine	17	0.64
Chida	2008	rac-Dihydroisocodeine	24	3.8
Hudlicky	2009	Codeine	18	0.19
Magnus	2009	rac-Codeine	13	20.1
Stork	2009	rac-Codeine	22	2.0
Fukuyama	2010	Morphine	18	4.8
Hudlicky	2011	ent-neopinone	15	46
Metz	2011	Codeine	23	47
Hudlicky	2013	Hudlicky hydrocodone	21	48
Hudlicky	2014	ent-codeine	15	49
Hudlicky	2014	ent-hydromorphone	12	50
Opatz	2014	Dihydrocodeine	14	51
Gaunt	2014	Morphine	25	52

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