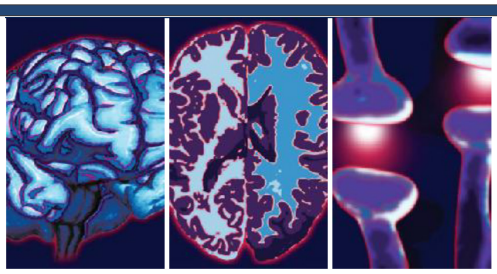
Research Article



The Mind Based and Most Controversial Plant: *Papaver somniferum* the Opium Poppy: A Plant with Many Faces and Roles in Human History and Culture.

Hamiksha†

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ABSTRACT

A typical cypriot ring bottom pitcher that resembles an upside-down pitcher *Papaver somniferum* seed pot that can be used bring opium to Egypt during the 18th dynasty. The opium poppy *Papaver somniferum* holds a significant place in human history and agriculture due to its diverse applications and controversial nature. The abstract delves into its historical significance, cultivation methods, genetic makeup, tissue culture techniques, policies, access across countries, patents, metabolites, traditional uses and pharmaceutical importance. Its history spans millennia, with ancient civilizations utilizing its narcotic properties for medicinal and recreational purposes. The etiology of *Papaver somniferum* involves understanding its genetic structure, life cycle and cultivation prerequisites. The plant exhibits different classes or varieties, each distinct in flower colour, alkaloid content and purpose. The differentiation of *Papaver somniferum* revolves around its cultivation practices and specific tissue culture techniques used for propagation and study. However, due to its potential for narcotics production, policies and regulations surrounding its cultivation and use are strictly controlled, varying significantly across different countries. Pharmaceutical access to *Papaver somniferum* is focused on deriving alkaloids like morphine and codeine for pain relief and anaesthesia. These metabolites play a key role in traditional and pharmaceutical uses, primarily in pain management and palliative care. Despite its medicinal significance, the regulated access reflects the constant balance between its benefits and potential risks associated with its narcotic properties.

Keywords: Opium, *Papaver somniferum*, metabolites, codeine, thebaine, noscapine, sanguinarine, papaverine, noscapine, alkaloids

Introduction

Papaver somniferum, is an annual flowering plant belonging to the Papaveraceae family. This plant is renowned for its striking flowers and its historical significance in the production of opium, a substance derived from its milky latex that contains alkaloids such as morphine and codeine.

The opium poppy is characterized by its delicate, papery flowers that come in various

Department of Genetic Engineering and Molecular Biology, Lovely Professional University, Punjab, India

†**Author for Correspondence:** Hamiksha, Department of Genetic Engineering and Molecular Biology, Lovely Professional University, Punjab, India
email: hamikshamomin@gmail.com

colours including shades of white, pink, red and purple [1-3]. It has a rich cultural and agricultural history, being cultivated for thousands of years for medicinal, culinary and recreational purposes. “The Omnivore’s Dilemma”, “How to Change Your Mind” and most recently, “This Is Your Mind on Plants,” serve as a poignant reminder that opium, despite its controversial nature, can occasionally bestow upon us a divine blessing. In the field of medical science, numerous surgical procedures would be rendered insufferable without the soothing touch of opium, while an opioid prescription can alleviate the anguish of a patient undergoing palliative care. It is imperative to acknowledge that opium, like any other substance, necessitates a comprehensive understanding of its historical significance, pharmacological properties and societal implications. Undeniably, these substances harbour inherent risks, leaving us perplexed as to how to cultivate a harmonious relationship with opiates. However, if we can unravel the enigma of integrating them safely and constructively into our society, drugs possess the potential to become invaluable tools with legitimate applications. Beyond its cultivation for opium, the plant has also been used in traditional medicine for its analgesic properties [4-6]. Its seeds are often employed in culinary practices, adding flavors, texture and nutrients to various dishes. The featured point to note that the plant’s components, particularly the opium extracted from it, are controlled substances due to their potent and potentially addictive nature and their use is regulated in most parts of the world. *Papaver somniferum*’s dual nature as both a source of pain-relieving substances and a subject of legal and ethical debate continues to make it a subject of interest in various fields, including medicine, agriculture and international drug policy [7,8].

▪ Overview

Research article on the opium poppy (*Papaver somniferum*), a plant with historical, medicinal and cultural significance, as well as potential for narcotic production. The article covers various aspects of the opium poppy, such as its etiology, classes, differentiation, policies, patents, metabolites, traditional uses and pharmaceutical access. The article highlights the dual nature of the opium poppy, as both a sourceinteres of important medicinal compounds and a subject of legal and ethical debate and the challenges of balancing its benefits and risks. The article provides a comprehensive overview of the opium poppy its history, cultivation, processing and uses and its implications for various fields, including medicine, agriculture and global drug policy.

▪ History

The opium poppy has been used in traditional medicine for thousands of years. Ancient Egyptian and Mesopotamian texts discuss opiate use for medical purposes, such as pain relief. In the Hippocratic tradition of ancient Greece, opium poppy was a frequent ingredient in many remedies in herbal medicine, the poppy flower is typically used to treat insomnia, anxiety and chronic pain [9,10]. The petals can be crafted into teas or made into tinctures and oils with healing properties [11,12]. Some cultures eat the seeds raw or add them to recipes for nutritious breakfasts, muffins and salads [13]. It’s important to note that while the opium poppy has medicinal value, its narcotic properties have led to misuse and addiction, which has resulted in a global drug problem [14,15]. Therefore, it is essential to use the plant and its derivatives responsibly and under medical supervision.

Methodology

▪ Ancient uses of opium poppy

The opium poppy (*Papaver somniferum*) is a plant with historical, medicinal and cultural significance, as well as potential for narcotic production. For countless millennia, the illustrious plant has gracefully intertwined itself within the tapestry of diverse human civilizations, dating back to the remarkable era of 5000 BC. Recognised for its diverse significance as a nourishing sustenance and a healing elixir, this botanical marvel has assumed a paramount position as a cherished emblem of traditional agriculture [9,16,17]. Nevertheless, in contemporary times the exploration of these functions has been overshadowed by the opulent indulgence in opium and its derivatives, along with the lucrative economies that flourish as a result.

The transformation of the opium poppy’s narcotic properties into a marketable commodity has been skillfully exploited by various influential individuals, using it

as a gateway to both wealth and political dominance [18,19]. The opium poppy has been used in traditional medicine for thousands of years. In the Hippocratic tradition of ancient Greece, opium poppy was a frequent ingredient in many remedies [20]. In herbal medicine, the poppy flower is typically used to treat insomnia, anxiety and chronic pain [21]. The petals can be crafted into teas or made into tinctures and oils with healing properties [22]. Some cultures eat the seeds raw or add them to recipes for nutritious breakfasts, muffins and salads.

▪ Processing of opium poppy (*Papaver somniferum*)

Opium poppy is an annual flowering plant that thrives in specific climatic conditions. It requires well-drained soil and moderate temperatures. The crop is generally sown in November and harvested in March-April. During the lancing operation, skilled workers make an incision on the poppy pod using a tool called "Nada." This process exudes a viscous substance with a high morphine content [23-25]. After lancing, raw opium is collected from the poppy pods. The collected opium is then dried either by heating or sun-drying. Drying is typically done at around 97°C-98°C for about five days, during which the morphine content gradually reduces [21,26]. The district opium officer receives the raw opium and tests it for purity and consistency [27]. Opium is classified into eight categories based on its consistency. Once tested, the opium is stored and graded. The enzyme peroxidase plays a vital role in the drying process. The next step involves synthesizing the opium's contents into finished heroin. This process transforms the mature but raw opium poppy plant into the potent drug [28,29]. The entire process is intricate and requires expertise. A key point to remember that opium poppy cultivation is strictly monitored and its use is regulated due to its potent alkaloids and potential for addiction.

▪ It is necessity of plant tissue culture for opium poppy

Plant tissue culture is a fascinating technique that has revolutionized the study of the opium poppy and its alkaloid production [30,31]. By cultivating plant cells or tissues in a controlled and sterile environment, researchers can delve into the specific details of opium alkaloid biosynthesis. This method has not only allowed scientists to understand the production of compounds like morphine and codeine, but it has also paved the way for the development of new opium poppy varieties with higher yields of these valuable substances [32,33]. Moreover, plant tissue culture has proven to be an invaluable tool in exploring the genetic diversity of the opium poppy. Through this technique, scientists have been able to unravel the secrets hidden within the plant's DNA, leading to the discovery of new methods for producing opium alkaloids [34]. The potential for innovation and advancement in this field is truly remarkable. However, it is essential to address the concerns associated with the use of plant tissue culture in opium alkaloid production. One worry is the possibility of overproduction, which could increase the global drug problem.

Also, there is a valid concern regarding the potential destruction of natural habitats and the loss of biodiversity that may result from this technique. Lastly, we must be cautious about the exploitation of farmers and other workers in the opium industry, as the use of plant tissue culture could potentially disrupt traditional farming practices. While plant tissue culture provides immense possibilities for scientific exploration and advancement, it is essential to approach its implementation with careful consideration and responsible practices [35]. By doing so, one can harness the power of this technique to solve the challenges of the opium poppy while ensuring the well-being of both the environment and the communities involved. Nanotechnology has opened up exciting possibilities in the realm of opium poppy research. The opium poppy, known scientifically as *Papaver somniferum* holds immense historical, medicinal and cultural significance, while also harbouring the potential for narcotic production. This plant has played a vital role in numerous human cultures, serving as both a source of sustenance and a valuable medicinal resource. Thanks to nanotechnology, we are now able to look into the complex biosynthesis of opium alkaloids like morphine and codeine, as well as to explore innovative methods for their production [36,37].

Furthermore, this innovative technique has enabled us to understand the genetic diversity of opium poppy and cultivate new varieties that yield higher quantities of these valuable compounds [38]. Nanotechnology has revolutionized the development of drug delivery systems, leading to significant

advancements in the effectiveness and safety of opium alkaloids. One remarkable breakthrough involves the creation of nanoparticles capable of encapsulating opium alkaloids and transporting them directly to specific cells or tissues within the body [39,40]. These nanoparticles protect the opium alkaloids from degradation in this way, increasing their bioavailability. [41]. This not only minimizes the risk of adverse side effects but also maximizes their therapeutic impact. Moreover, nanotechnology has also played a pivotal role in the detection of opium poppy cultivation and the monitoring of the global drug trade [42].

Researchers have utilised the power of nanotechnology to devise innovative methods for identifying opium poppy growth and tracking the illicit drug market [43]. The potential of nanotechnology in the study of opium poppy is truly promising. It has been instrumental in exploring the biosynthesis of opium alkaloids, developing advanced drug delivery systems and uncovering opium poppy cultivation. However, it is essential to acknowledge that the use of opium alkaloids comes with legal and ethical concerns. Misuse or abuse of these substances can lead to addiction and various health complications. Therefore, while nanotechnology provides immense possibilities in this field, responsible and ethical practices must be upheld to ensure the well-being of individuals and society as a whole [44].

▪ Metabolites of the opium poppy (*Papaver somniferum*)

These specialized metabolites are responsible for the medicinal properties of opium poppy. Key bias include;

Morphine: A potent narcotic analgesic used for pain relief. Morphine, a potent opiate, is naturally found in opium, a dark brown resin produced by drying the latex of opium poppies (*Papaver somniferum*) [45]. Morphine is an exceptional analgesic that is primarily used for the relief of pain. Its effectiveness in managing both acute and chronic pain makes it a valuable medication in various medical conditions. It is particularly beneficial in alleviating pain caused by myocardial infarction, kidney stones and during labor [46,47]. Morphine gives multiple administration routes, providing flexibility in delivering the medication to patients. It can be administered orally, sublingually, *via* inhalation, injection (intramuscular, intravenous, epidural and intrathecal), trans dermally, or as a rectal suppository [48].

This wide range of options ensures that healthcare professionals can choose the most suitable route based on the patient's condition and needs. Understanding the pharmacokinetics of morphine is essential in optimizing its therapeutic effects. The bioavailability of morphine varies depending on the route of administration, with approximately 20%-40% when taken orally, 36%-71% rectally and 100% when administered intravenously or intramuscularly [49,50] The onset of action is relatively fast, with effects observed within 5 minutes when given intravenously, 15 minutes intramuscularly and 20 minutes orally. The duration of action ranges from 3 to 7 hours, providing sustained pain relief [51,52]. Metabolism primarily occurs in the liver, while excretion predominantly takes place through the kidneys (90%) with a smaller portion eliminated through the bile ducts (10%) [53,54]. By providing various administration routes and demonstrating favourable pharmacokinetic properties, morphine proves to be a versatile and effective medication for pain management.

Its ability to provide relief in different types of pain, along with its reliable onset and duration of action, makes it an invaluable tool in the hands of healthcare professionals [55]. The breakthrough in this research occurred when scientists identified specific poppy plants that were unable to produce morphine or codeine. Instead, these plants accumulated a different compound called *(S)*-reticuline. It was discovered that these plants carried mutations in the *STORR* gene, which caused a disruption in the pathway to morphine production in poppy plants. The *STORR* gene plays a key role in encoding the enzyme responsible for catalyzing the initial step in the pathway to morphine production. This enzyme converts the precursor molecule *(S)*-norcocaine into *(S)*-reticuline, which then undergoes further conversions to eventually lead to morphine production. The identification of the *STORR* gene and its involvement in morphine biosynthesis has significant implications. It could potentially aid researchers in developing innovative approaches for producing morphine and other opioids.

Codeine: Another analgesic with milder effects. Codeine, a significant alkaloid derived

from the opium poppy (*Papaver somniferum*), is an opiate and a pro-drug of morphine. It is naturally found in the sap of the opium poppy. Codeine is commonly prescribed to alleviate mild to moderate pain. The best cough suppression it is also utilized as a cough suppressant in various liquid preparations [34]. It has conversion to morphine within the body, codeine undergoes a conversion process facilitated by an enzyme in the liver, resulting in the formation of morphine [56]. Codeine is the most commonly used opiate in the world. It can be extracted from the plant, but most of it is made from morphine which is a natural painkiller in humans and more plentiful in the opium poppy. Codeine also has antimicrobial properties. However, codeine abuse can be very dangerous and cause addiction, overdose or death. People under 18 years old should not use codeine. Moreover, codeine can harm your baby if you are pregnant, as it can cause severe withdrawal symptoms.

Noscapine: The opium poppy (*Papaver somniferum*) is the source of a remarkable alkaloid called noscapine, which has a rich history and a wide range of uses. For years, noscapine has been a trusted antitussive (cough suppressant) that does not cause addiction, sedation or euphoria like other opioids. It works by affecting the brain's cough center and helps with various respiratory problems. Noscapine also has anticancer potential, as shown by recent studies. By disrupting microtubules, water-soluble noscapine analogues can stop cancer cells from growing better than noscapine itself [57]. These analogues, along with improved drug delivery systems, have proven effective in treating different conditions in animal models, such as Parkinson's Disease (PD), Poly-Cystic Ovary Syndrome (PCOD), Multiple Sclerosis (MS) and more. Since noscapine can cross the blood-brain barrier, it may also help with brain and mental disorders. Noscapine is widely available, easy to use and has a long history of safety, making it a perfect candidate for curing many serious diseases [58]. Moreover, noscapine may have a role in fighting COVID-19, as it can bind to the Main protease (Mpro) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-cov-2) paving the way for possible combination therapies [59].

Thebaine: Thebaine or paramorphine, is a pharmacological marvel. It stands out from other opioids like morphine and codeine as it stimulates rather than sedates. This makes it a rare and interesting substance. Thebaine can cause seizures at high doses, similar to strychnine poisoning. This shows how powerful and complex this substance is. Thebaine is very important for the industry. It is the key ingredient for making various painkillers, such as the famous drugs Oxycodone, Hydrocodone, Naltrexone and Naloxone. These drugs help to ease pain and fight opioid addiction and overdose [60]. However, thebaine is not a legal substance everywhere thebaine is closely related to other alkaloids like salutaridine, oripavine, morphine and reticuline [61]. This complex network of links shows how these substances are connected and how they can be further studied and researched (Figure 1).

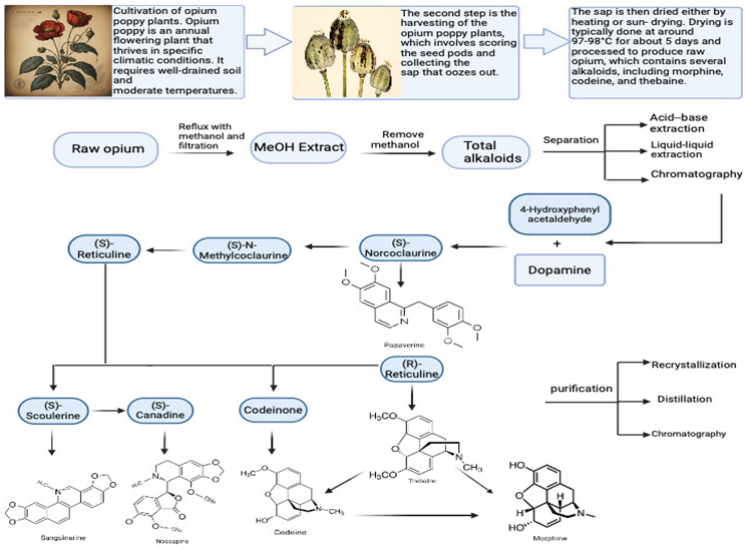
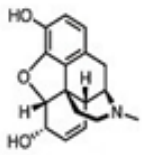
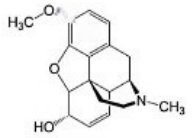
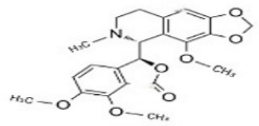
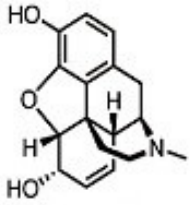
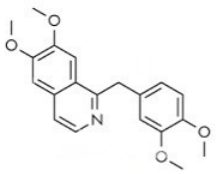
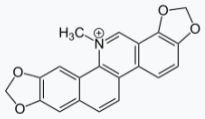


Figure 1. A flowchart representing the synthesis and extraction of morphine.

Papaverine: Papaverine is a significant alkaloid that comes from the opium poppy (*Papaver somniferum*). It is part of a group of opium alkaloids that also includes morphine, codeine, thebaine, noscapine and narceine. Papaverine has a vital role in medicine and pharmacology. To get opium, the opium poppy's green seed pods are cut carefully. A white latex liquid comes out of the cut and turns brown when it touches the air. This liquid is scraped off, dried and made into an opium cake that has at least 10% morphine by weight. The opium poppy has a long and rich history, with traces of its use going back to ancient times. The Sumerians, who lived in the area between the Tigris and Euphrates Rivers (Mesopotamia), were some of the first people to grow and use opium. They called it the "plant of joy" and gathered the white liquid that leaked from the poppies. Papaverine and other alkaloids make the opium poppy a remarkable plant that has a lasting impact on medicine and human history (Table 1).

Table 1: Comparative overview of bioactive metabolites and their medicinal properties.

Sl.No	Metabolites	Medicinal properties	Structure
1	Morphine $C_{17}H_{19}NO_3$	Analgesic, sedative. It is particularly beneficial in alleviating pain caused by myocardial infarction, kidney stones and during labour	
2	Codeine $C_{18}H_{21}NO_3$	Analgesic, cough suppressant it is antimicrobial in nature	
3	Noscapine $C_{22}H_{23}N_O7$	Antitussive, anticancer. Since noscapine can cross the blood- brain barrier, it may also help with brain and mental disorders	
4	Thebaine $C_{19}H_{21}NO_3$	Analgesic, antitussive. It is the key ingredient for making various painkillers	
5	Papaverine $C_{20}H_{21}NO_4$	Vasodilator, antispasmodic	
6	Sanguinarine $C_{20}H_{14}NO_4$	Antimicrobial, anti- inflammatory	

Metabolic regulation: The production of bias is tightly regulated within the plant. Flux modulation occur through primary metabolism including glycolysis, the tricarboxylic acid cycle, Nitrogen assimilation and Phospholipid or fatty acid synthesis all of which generate secondary metabolic precursors [62,63].

Preparation of secondary metabolites: The process of preparing secondary alkaloids of opium poppy involves several steps. The first step is the cultivation of opium poppy plants, which are grown in specific regions of the world for pharmaceutical and food purposes then it is the harvesting of the opium poppy plants, which involves scoring the seed pods and collecting the sap that oozes out [64,65]. The sap is then dried and processed to produce raw opium, which contains several alkaloids including morphine, codeine and thebaine after that the extraction of the alkaloids from the raw opium is done. This is typically done using a solvent extraction method, which involves dissolving the raw opium in a solvent, such as ethanol or methanol and then filtering the solution to remove impurities. The alkaloids are then separated from the solvent using various techniques such as acid-base extraction, liquid-liquid extraction, or chromatograph and the last step is the purification of the alkaloids. This is typically done using various techniques, such as recrystallization, distillation, or chromatography. The purified alkaloids can then be used for various purposes such as the production of pharmaceuticals or the synthesis of new compounds. In summary, the process of preparing secondary alkaloids of opium poppy involves several steps, including cultivation, harvesting, extraction and purification. The alkaloids can be used for various purposes such as the production of pharmaceuticals or the synthesis of new compounds [9,66,67].

Results and Discussion

▪ Legal and ethical aspects related to the opium poppy (*Papaver somniferum*)

Types of licenses: Opium cultivation licenses are granted for two primary purposes. Obtaining opium gum through lancing involves collecting raw opium from the poppy pods [68]. Production of poppy straw from unlanced opium poppy in this poppy straw contains alkaloids and is used for medicinal purposes [69]. The licensing policy specifies conditions for granting licenses, including yield requirements, area limits and quality standards. The government monitors the entire process to prevent misuse and diversion. Nevertheless, in contemporary times the exploration of these functions has been overshadowed by the opulent indulgence in opium and its derivatives, along with the lucrative economies that flourish as a result. The transformation of the opium poppy's narcotic properties into a marketable commodity has been skillfully exploited by various influential individuals, using it as a way to both wealth and political dominance [70].

The opulent government graciously informs designated parcels of land where the cultivation of opium can be granted a prestigious license on an annual basis. These esteemed notifications are commonly known as opium policies, a testament to the government's careful attention to detail. In select states, the cultivation of opium is permitted solely within the boundaries of these notified tracts. Cultivators, aspiring to partake in this esteemed endeavor, must surpass the lofty standard of the Minimum Qualifying Yield (MQY) to prove their worthiness for a license in the forthcoming year. The revered Central Bureau of Narcotics (CBN) takes on the noble responsibility of issuing licenses to deserving farmers, ensuring that each field remains within the confines of the licensed area, thus upholding the sanctity of this esteemed trade [71].

Opium poppy cultivation in India is strictly regulated and legal, but only for medical and scientific purposes. The cultivation of opium poppy is authorized and controlled by the Narcotic Drugs and Psychotropic Substances (NDPS) Act, which grants the Central Government the authority to grant permits and oversee the cultivation process [72]. Every year, the Government of India issues notifications, known as opium policies, specifying the areas where opium cultivation can be licensed and outlining the general conditions for obtaining a license. Currently, opium cultivation is allowed in the designated tracts located. The Central Bureau of Narcotics (CBN) in Gwalior, Madhya Pradesh, operates under the supervision of the narcotics commissioner and is responsible for issuing licenses to farmers who wish to cultivate opium poppy. To ensure compliance with the licensed area, CBN officers carefully measure

each field owned by the cultivators (Figure 2). Additionally, the cultivators are obligated to sell their entire opium yield to the CBN and the government determines the price at which they are compensated [73]. While officially illegal, there is an informal acceptance in some regions. Possessing and consuming opium poppy seeds is legal, but growing the plant is illegal. Cultivating opium poppy plants is considered a federal crime. Opium poppy cultivation raises several ethical concerns due to its historical significance, medicinal properties and potential for misuse.

Opium contains morphine, a potent opioid. Its misuse leads to addiction, overdose and societal harm. Ethical questions arise around promoting a crop with such risks. Opium has played a significant role in both past and present epidemics of opioid addiction and fatal overdose incidents [74]. However, it is important to note that in India, the cultivation of opium poppy is strictly regulated and legal only for medical and scientific purposes. The Narcotic Drugs and Psychotropic Substances (NDPS) Act grants the central government the authority to authorize and oversee the cultivation of opium poppy [75,76]. Each year, the Government of India releases notifications known as opium policies, which specify the areas where opium cultivation can be licensed and outline the general conditions for obtaining a license. Large-scale cultivation affects biodiversity, soil health and water resources. Balancing economic gains with ecological sustainability is vital. Opium cultivation has a profound effect on the environment, as identified in a report by the Transnational Institute. This report emphasizes that opium cultivation poses an environmental crisis in countries like Myanmar, where it is extensively grown.

The detrimental impacts of drugs such as cannabis, cocaine, opium and ecstasy on the environment are catastrophic, ranging from deforestation to land sinking. In India, the cultivation of opium poppy is strictly regulated and legal, but solely for medical and scientific purposes. The Narcotic Drugs and Psychotropic Substances (NDPS) Act grants the central government the authority to authorize and oversee opium poppy cultivation [77]. Each year, the Government of India designates specific areas where opium cultivation can be licensed and they also establish the general conditions for issuing licenses. Poppy farmers often face stigma due to drug associations. Ethical discussions involve supporting livelihoods without perpetuating negative stereotypes [78,79]. Opium cultivation licenses are granted for two primary purposes are obtaining opium gum through lancing, production of poppy straw from unlanced opium poppy [80].

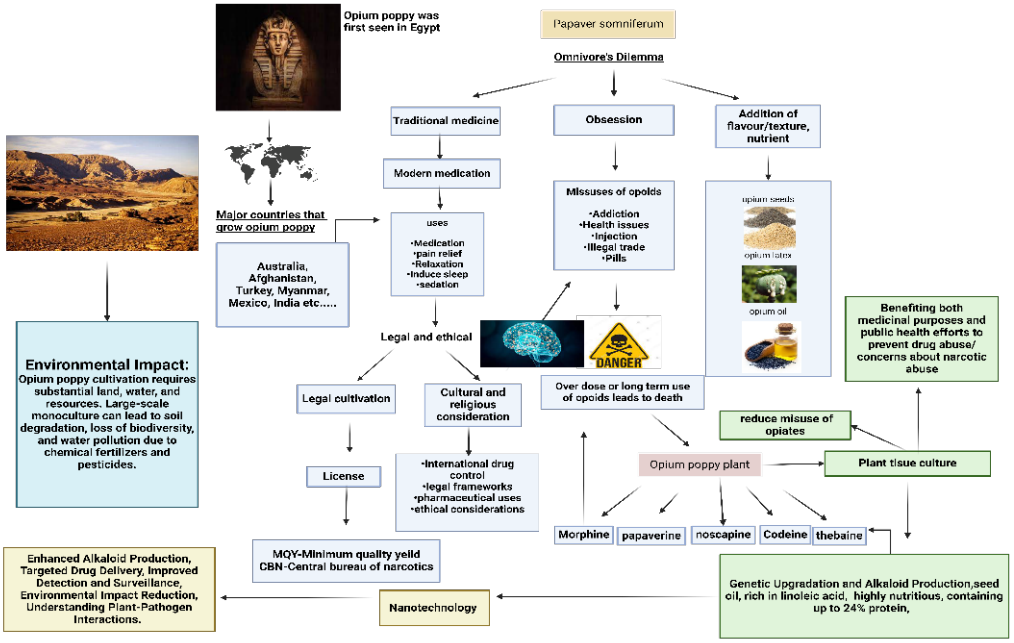


Figure 2. A flowchart representing the synthesis and extraction of morphine.

General conditions: The licensing policy specifies conditions for granting licenses including yield requirements, area limits and quality standards [81]. The government monitors the entire process to prevent misuse and diversion. International trade controls refer to governmental regulations that influence the flow of goods and services across national borders [82]. These controls serve various purposes including protecting domestic industries, managing risks and maintaining economic stability [83,84].

Exchange control: Exchange control involves restrictions on private transactions in foreign exchange. It aims to prevent unfavorable payment imbalance by limiting foreign exchange purchase to match receipts. For this governments use methods such as licensing, quotas and exchange rate management. Protective devices like countries employ several protective measures, subsidies to domestic producers, import taxes, quantitative restriction of limiting the quantity of specific imports, state trading, terms of trade, demand restriction, supply restriction [85,86].

International trade law: Rules governing trade between nations. It provides a frame work for resolving disputes and ensuring fair practices. The United Nations single convention on narcotic drugs of 1961 is responsible for regulating the global trade of opium poppy [87]. This convention not only prohibits the unauthorized cultivation of the opium poppy but also governs various aspects such as production, manufacturing, export, import, distribution, trade, use and possession of opium, morphine, cocaine and cannabis. To ensure compliance with its regulations, the convention established the International Narcotics Control Board (INCB) as a monitoring and enforcement body. Furthermore, in 1953 the protocol for limiting and regulating the cultivation of the poppy plant, the production of international and wholesale trade in and use of opium was signed in New York city [88,89]. This protocol aimed to impose more stringent controls on opium production and regulate its international trade.

▪ Drug controlled scheduled levels

Level 1 schedule is an executive summary of the overall schedule. Often presented as a milestone list or a project master schedule. Drugs with no accepted medical use and high potential for abuse [90]. Examples: Heroin, Lysergic acid diethylamide (LSD), marijuana and level 2 schedule is a management summary that consolidates hazardous. Includes information from the level 1 plan. Helps executives decide whether to move forward with the project [91,92]. Examples include morphine, oxycodone and fentanyl. But in level 3 drugs have a lower abuse potential compared to schedule I and schedule II drugs, but a higher abuse potential compared to schedule IV drugs [93]. It includes drugs include products with less than 90 milligrams of codeine per dosage unit, ketamine, anabolic steroids and testosterone.

The level 4 schedule drugs, substances, or chemicals are categorized as having a low likelihood of abuse and a low potential for dependence [94]. Here are a few schedule IV drugs such as xanax, soma, darvon, darvocet, valium, Aaivan, talwin, ambien, tramadol and the level 5 schedule the most granular level that provides detailed breakdowns. These drugs can include cough preparations containing less than 200 milligrams of codeine per 100 millilitres as well as Lomotil, Motofen, Lyrica and Parepectolin. The opium poppy (*Papaver somniferum*) has a rich history and is known for its fascinating secondary metabolites. Let's examine into the advantages and potential drawbacks associated with this extraordinary crop.

Medicinal alkaloids: The opium poppy produces various medically significant alkaloids, such as morphine, codeine and thebaine. These compounds are widely used in modern medicine as effective pain relievers, cough suppressants and muscle relaxants. Morphine, in particular, is renowned as one of the most potent painkillers globally. Opium poppy, scientifically known as *Papaver somniferum*, has been cultivated for therapeutic purposes for almost eight thousand years. This flowering plant possesses medicinal properties due to specialized metabolites called Benzylisoquinoline Alkaloids (BIAs). These BIAs include powerful painkillers like morphine and codeine, as well as the antimicrobial agent sanguinarine and the potential anticancer drug noscapine [95]. Moreover, thebaine, a naturally occurring compound is utilized in the semi-synthesis of widely prescribed pain-relievers such as oxycodone and hydrocodone [96].

It is also employed in valuable drugs for the treatment of opioid addiction, like naltrexone and as an antidote for opioid overdose, such as naloxone [97]. The biosynthesis of BIAs in opium poppy is a complex process that involves multiple enzymatic steps. Recent advancements in functional genomics have allowed for the identification of a nearly complete set of BIA biosynthetic genes, many of which are clustered in the opium poppy genome. Synthetic biology has also made significant progress, enabling the successful reconstruction of several BIA biosynthetic pathways in different hosts like *Saccharomyces cerevisiae* and *Escherichia coli* [98]. However, the initial low production levels indicate that scaling up production for commercial purposes will pose additional challenges.

Poppy seeds: When the dried pods of the opium poppy are crushed, they yield poppy seeds also known as "khus khus" locally [99]. These seeds are commonly used as a spice in Indian cuisine and currently hold a high market value. Poppy seeds are a nutrient-dense ingredient that provides a variety of essential minerals, including thiamine, folate, calcium, iron, magnesium, manganese, phosphorus and zinc. They are also a good source of dietary fiber and contain healthy fats like omega-3 fatty acids. In a 100 gm serving, poppy seeds provide 525 calories and have a composition of 6% water, 28% carbohydrates, 42% fat and 21% protein [100,101]. These versatile seeds can be used in their whole form or ground into a meal to enhance the flavor and texture of various dishes. They are commonly used in pastry and bread recipes and can also be pressed to extract poppy seed oil.

Regulation and monitoring: Opium cultivation in India is strictly regulated and closely monitored. It is legally grown only in three states; Madhya Pradesh, Rajasthan and Uttar Pradesh exclusively for medicinal and scientific purposes. The Indian government issues licenses to farmers, allowing them to cultivate opium poppy on designated land parcels. The crop is sown in November and harvested between March and April. Growing poppy requires significant time and labor. Skilled workers perform lancing operations to extract the viscous substance with a high morphine content from the poppy pods. A research paper titled "Cellular Localization of Morphine Biosynthesis in Opium Poppy: Insights from immunofluorescence labelling and shotgun proteomics" this paper utilizes immunofluorescence labelling and shotgun proteomics techniques to determine the specific cell types involved in the biosynthesis of morphine in opium poppy. According to the findings, the initial step of morphine biosynthesis, the conversion of (R)-reticuline to salutaridine takes place exclusively in sieve elements [102,103].

These sieve elements serve as the channels for transporting sugars and other metabolites over long distances. Subsequent steps of morphine biosynthesis from salutaridine to morphine, predominantly occur in laticifers. Laticifers are specialized cells responsible for producing and storing latex, which contains high concentrations of alkaloids. The paper also proposes a model for the intercellular transport of intermediates between sieve elements and laticifers. Overall, the combined use of immunofluorescence labelling and shotgun proteomics has significantly advanced the understanding of the cellular localization of morphine biosynthesis in opium poppy. Furthermore, the National Research Centre for Medicinal and Aromatic Plants (NRCMAP) has published a research paper titled "Research Achievements in Opium Poppy: Insights from the All-India Coordinated Research Project on Medicinal and Aromatic Plants". This paper presents the notable research accomplishments of the All-India Coordinated Research Project (AICRP) on Medicinal and Aromatic Plants in the field of opium poppy. The research encompasses various aspects such as germplasm resources management, crop production, plant protection and more.

▪ Opium plant consideration as a most lethal drug

Opioids, the epitome of opulence in the realm of pain relief possess an unparalleled efficacy. However, their allure is accompanied by a treacherous addiction. Once the go-to remedy for acute agony stemming from invasive surgeries, combat trauma, vehicular mishaps and the harrowing clutches of end-stage cancer, opioids gradually infiltrated the field of chronic pain management approximately two decades ago [104]. As the grip of painkiller addiction tightened its hold, physicians adopted a more stringent approach to prescribing these potent substances. Consequently, a multitude of individuals found themselves denied of their much-needed comfort, only to be enticed

by the siren call of cheap, unadulterated heroin lurking on the street corners. Whether ingested, insufflated or injected, opioids are greeted with open arms by the human body. These pharmaceutical marvels ingeniously tap into our innate pain-alleviating mechanisms, artfully mimicking the effects of natural opioids like endorphins [105]. These endogenous opioids spring into action when the body is subjected to pain or injury, soothing the torment, slowing the rhythm of breath and heartbeat and in certain instances, causing a euphoric state [106]. Opioid receptors, scattered throughout the central nervous system, awaken in the aftermath of tissue damage caused by an injury, rendering more receptors available for engagement [107]. Patients afflicted by severe injuries can endure substantial doses of opioids without succumbing to overdose. However, the very same dosage employed to moderate pain following a catastrophic trauma can effortlessly transform into a lethal overdose once the individual in question is no longer tormented by agony [108].

This metamorphosis occurs as the opioids bind to other unoccupied receptors within the brain, inducing a state of euphoria and at higher doses, suppressing vital autonomic functions such as respiration. Numerous scholars of eminence firmly uphold the notion that a plethora of addictive substances such as heroin, methadone, cocaine, nicotine and even alcohol, share similar physical mechanisms. Each of these substances binds to receptors that instigate a surge in the neurotransmitter dopamine within the brain's reward centre, a diminutive cluster of neurons nestled in the nucleus accumbens, situated in the central region of the brain. Dopamine nerve cells play a pivotal role in various facets of gratification, encompassing the preliminary stage of anticipation, the exhilarating rush experienced during consumption and the subsequent recollection of pleasure. As the consumption of these substances persists, the brain gradually acclimates to the abnormal levels of dopamine and other neurotransmitters within the nucleus accumbens, as well as other cerebral domains, including the frontal cortex, the amygdala, the hippocampus and the locus coeruleus [109]. These alterations amplify the activity within brain regions responsible for reward and impulsive behavior, while simultaneously dampening the functioning of regions associated with judgment, long-term planning and self-control, as elucidated by Madras. Remarkably, these transformations bear a striking resemblance to the ongoing developmental processes transpiring within the adolescent brain, which renders teenagers particularly vulnerable to the clutches of addiction.

▪ Harms and risks

Narcotic properties, the dried pod of the opium poppy, known as "dodachura" locally, possesses mild narcotic properties. It is sometimes illegally traded on the black market at exorbitant prices. Consumption of food containing contaminated poppy seeds can lead to unintentional intoxication and false positive drug tests [110]. Some individuals may intentionally use opiates derived from contaminated seeds for intoxication or claimed health benefits, including pain relief and anxiety treatment. Consuming large quantities of contaminated poppy seeds as tea can result in overdose and even death. Disasters such as sunshine, hail and frost, he also has to suffer from many insects, birds and other animals [111]. Fungi and viral diseases also play their part. As soon as the seeds germinate and the seedlings sprout two to four leaves, a small insect known as Dhirkuor Gadhiya starts the trouble. This insect jumps from plant to plant and cuts off the young terminal taxon, as a result the plant cannot grow normally. The cutworm often destroys growing crops. The cricket *Gryllotalpa vulgaris* is often a very serious pest, cutting off mandibular plants that are almost fully grown [112]. Moth larvae are also important enemies of growing poppies rats, rabbits, monkeys, blue bulls and parrots also destroy crops significantly [113]. A poor farmer must save his crops from monkeys and parrots by day and rabbits and blue bulls by night.

▪ Genetic improvement and crop improvement

Genetic diversity and the enhancement of opium poppy crops are vital areas of study that contribute to the advancement of varieties with desirable characteristics such as increased alkaloid content, resistance to diseases and improved yield. Below is an in-depth examination of the current research poppy germplasm [114,115]. This investigation identified five distinct sub-populations with unique genetic traits, providing valuable

resources for genetic enhancement.

Techniques in plant breeding: The implementation of various plant breeding techniques has resulted in the improvement of opium poppy genetics. This includes the development of new varieties through traditional breeding methods and the utilization of mutagenesis to create non-narcotic variants [116,117].

Detection of genome-wide single nucleotide polymorphism: Genotyping by sequencing continues to be the preferred method for detecting genome-wide Single Nucleotide Polymorphisms (SNPs) in opium poppy [118]. This is essential for comprehending the genetic composition and facilitating breeding purposes.

Superior genotypes and hybrid vigor: Research indicates that isolating superior genotypes through selective breeding and recurrent selection, as well as utilizing the benefits of hybrid vigor in specific parental-cross combinations are effective strategies for enhancing crop quality [119, 120].

Mutation breeding: Mutation breeding has played a significant role in the development of varieties such as 'Sujata' which is non-narcotic and free of alkaloids [121]. This approach is expected to be instrumental in creating customized crop varieties to meet future demands in medicinal and aromatic crops.

▪ New varieties and cultivation techniques in opium poppy

Research in opium poppy is focused on enhancing yield, alkaloid content and disease resistance through the exploration of new varieties and cultivation techniques. Notably, the All-India Coordinated Research Project (AICRP) on Medicinal and aromatic plants has introduced six high latex yielding varieties of opium poppy [122,123]. Additionally, the AICRP has established standardized agro techniques and disease management strategies to boost crop productivity. In India, the cultivation of opium poppy is regulated by the narcotics commissioner, with the government announcing the licensing policy annually. Currently, cultivation is permitted in specific regions of Madhya Pradesh, Rajasthan and Uttar Pradesh. Technological advancements, such as concentrated poppy straw technology, offer mechanized methods for harvesting poppy gum, potentially increasing efficiency [124,125] For a comprehensive understanding of the latest research and developments in opium poppy cultivation, detailed publications and reports from reputable research institutions are available as valuable resources.

▪ Genome wide SNP detection in opium poppy

Genome-wide SNP detection in opium poppy is an essential area of research that offers valuable information into the genetic diversity and potential for enhancing crop quality. Recent studies have revealed many things as by utilizing this method, researchers have successfully explored the genetic diversity and population structure within opium poppy germplasm [126]. This approach has identified five distinct sub-populations, providing valuable resources for genetic enhancement. The development of Simple Sequence Repeats (SSR) and SNP markers has proven instrumental in distinguishing opium poppy from other *Papaver* species [127]. These markers play a vital role in breeding programs, enabling targeted improvements. The analysis of genetic diversity also encompasses the study of alkaloid profiles, which exhibit significant diversity, with morphine being the predominant compound [128]. Understanding the secondary metabolism of the plant is vital for further research. The development of new SNP loci through simplified gene sequencing technology has revolutionized the identification of opium poppy and its related species. This advancement holds great importance in legal cultivation and the control of illicit trafficking. These recent findings contribute significantly to our understanding of opium poppy genetics and pave the way for future advancements in crop improvement.

▪ Technological advancements in opium poppy

Concentrated poppy straw technology: This innovative method involves mechanized processes for harvesting opium gum [129]. It reduces the need for labor and time during extraction, while also increasing the yield and purity of the product. A new technique utilizing SNP loci, this approach accurately identifies opium poppy and its related species. It enables legal cultivation and aids in controlling illicit trafficking by distinguishing opium poppy from other *Papaver* species [130]. Deep learning

object detection, this novel approach utilizes remote sensing images to detect opium poppy parcels. By employing a Single Shot Multi-box Detector (SSD) model, it precisely locates the exact coordinates of opium poppy cultivation patches [131,132]. Notably, it eliminates the need for manual feature extraction and achieves a high recognition rate.

Conclusion

The opium poppy, scientifically known as *Papaver somniferum*, has an interesting and complex history deep intertwined with different aspects of human society. Its origin, genetic composition and life cycle all contribute to its cultivation and wide range of uses. This plant is known for its various classes or varieties, which are distinguished by characteristics such as alkaloid content, flower color and intended purpose. The differentiation of *Papaver somniferum* relies on specific cultivation techniques, processing methods and tissue culture practices used for propagation and study under controlled conditions. The cultivation and use of this plant are governed by policies that vary across different countries due to its potential for narcotic production. Patents related to the opium poppy typically focus on specific methods or innovations in cultivation, processing, or use rather than patenting the plant itself. The plant's metabolites particularly alkaloids like morphine and codeine, form the basis for numerous traditional and pharmaceutical applications, particularly in pain relief and anaesthesia. The opium poppy has been used for centuries in traditional medicine, cultural practices and even culinary purposes. In the pharmaceutical industry, *Papaver somniferum* is primarily utilized for extracting alkaloids essential in pain relief, anaesthesia and palliative care.

In conclusion, the significance of *Papaver somniferum* lies in its rich historical, medicinal and cultural importance, while its access and policies reflect the delicate balance between its medicinal benefits and the potential risks associated with its narcotic properties. The alkaloids derived from this plant play a vital role in alleviating pain and contribute to various pharmaceutical applications, there by aiding the medical industry's efforts to manage pain and enhance patient care. Recent advancements in opium poppy research include the development of high-yielding and disease-resistant varieties, the introduction of efficient and pure harvesting methods, the use of simplified gene sequencing and deep learning object detection techniques for identification and the acquisition of valuable information into genetic diversity and alkaloid profiles through genotyping by sequencing and genome-wide SNP detection.

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