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The opium poppy (*Papaver somniferum* L.): Historical perspectives recapitulate and induced mutation towards latex less, low alkaloids in capsule husk mutant: A review

RK Lal

Abstract
One of the oldest plants known to humans is the opium poppy (*Papaver somniferum* L.). It's where opium and opium alkaloids come. By 4000 BC, Sumerians had discovered its therapeutic, nutritional, and narcotic properties, and by 1400-350 BC, Greeks had discovered it. Mutagenesis significantly suppresses enzyme function, weakening or blocking secondary metabolite production. Opium and opium-alkaloids, particularly morphine, are addictive opioids in the opium poppy, leading to serious global drug misuse. In the straw mutant LL-34, the genetic conversion of latex 'opium poppy' into latex less seed poppy' resulted in opium less and very low alkaloids variety Sujata. This publication reviews and describes the nature and kind of specific effective mutations previously achieved at the CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow (India). Medicinal and aromatic crops were recently introduced to the mutant breeding program, maybe in the 1980s in India. Nonetheless, there have been notable achievements, some of which may be one-of-a-kind. At CSIR-CIMAP, Lucknow (India). Coordinated efforts were made for genetic tailoring (restructuring) of the plant frame, enhanced seed productivity in *Papaver somniferum* L., and weak or absent latex biosynthesis (Opium poppy). Several qualitative macro alterations, such as an opium-free oil-seed variety of opium poppy Sujata, have been developed for commercial use. The abundant quantitative variation was also created by reshuffling the polygenic background in both seed and vegetatively propagated medicinal and aromatic crops (MACs), and then superior varieties were evolved and released after a rigorous screening in the field evaluation or the pipeline for release using the mutation breeding approach. The opium poppy varieties Sujata and Vivek are notable.

Keywords: Concentrated poppy straw, golden triangle, gamma irradiation, mutation breeding, opium

Introduction
Opium poppy (*Papaver somniferum* L.) - The source of opium and opium alkaloids is one of the most ancient plants known to human beings. Sumerians' medicinal, food, and narcotic properties were known to 4000 BC and Greeks by 1400-350 BC (Husain and Sharma, 1983) [15]**.** The opium poppy was cultivated in Rome during the 6th century BC and in Egypt during Arab rules in the 700 AD; while in India, its cultivation was established by the 16th century BC (Husain and Sharma, 1983) [15]. Britishers expanded their cultivation substantially. Currently, the legal cultivation of opium poppy is restricted in the three adjoining states of India, *viz*., Uttar Pradesh, Madhya Pradesh, and Rajasthan. Since the Mughals introduced the opium poppy through British rules, strict governmental control has been exercised in India. No one can grow even a plant of opium poppy without a proper license issued by the Central Bureau of Narcotics (CBN), Govt. of India. A close watch and vigilance on legitimate growers are maintained until the opium extraction is over and deposited with the Narcotics Department (ND) every year. Defaulters are penalized, and their licenses are forfeited (Sharma *et al*., 2002a) [28].

As an opium and opium alkaloid source, the opium poppy is a narcotic crop. Therefore, India's area under cultivation is highly controlled through a complicated and lengthy administrative process of issuing legal licenses. Even though it is also a source of poppy seeds (*posta dana*/*khas-khas*) — a precious export commodity, expanding its area for seed production is hazardous because of the risks involved in opium abuse. However, this can be overcome by growing a nonnarcotic poppy (devoid of opium) purely as a seed crop. The newly evolved novel opium less with shallow alkaloid profile mutant seed variety Sujata

(Sharma *et al*., 1999a, b) [27, 30] can be grown in an extensive area without the risk of opium abuse and the tedious licensing process.

Origin and botanical description of the plant

Opium poppy (*Papaver somniferum* L., 2*n* = 22) is a herbaceous plant belonging to Papaveraceae. Based on its native distribution and the range of genetic variation, this species is considered to have originated in the Mediterranean coastal region (Husain and Sharma 1983, Bernàth 1998) [15, 4]. However, it is widely scattered worldwide, extending up to 60º N in the northwest (erstwhile) of the Soviet Union and the southern limit reaching almost the tropics (Veselovskaya, 1976) [41].

Usually annual, the poppy plant grows erect, commonly 50 to 120 cm tall with a pithy stem. Some forms in India's Malwa region may be 120-150 cm tall with fewer branches (often monopodial), each with solitary flowers on a long pedicle/stalk (Puri 1983) [25]. Rosette leaves are usually petiolated. The radical leaves are elongated and irregularly lobed, upper leaves more or less sessile. Lemina is entirely incised, sometimes deeply fringed (Sharma *et al*. 1992) [32]. Flowers are bisexual with four petals of varying exquisite colors — the cultivated forms in Uttar Pradesh generally possess white and Madhya Pradesh and Rajasthan scarlet red petals. The opium poppy is a highly cross-pollinated crop. But some opium poppy genotypes have come under the often cross-pollinated or cleistogamous categories. Self-pollination predominates with 10-30% outcrossing in the often cross-pollinated plants (Sharma and Singh 1983). After the flowering is over (petals fall within a week of anthesis), the peduncle (10-15 cm long) bears the poppy capsule (fruit), which may be of different shapes and sizes. The capsule contains one to two thousand remiform and generally white seeds – off-white, greyish-white is also common — which are thrashed out from the dried capsules (Figure 1). The remaining capsule hulls are useful as they contain opium alkaloids, though infractions.

Development and distribution of laticiferous system – Locale for latex (opium) biosynthesis in plant

Papaver somniferum is one of the several latex-bearing species in the plant kingdom. But unlike others where the whole body cells contain latex, in the opium poppy, latex (raw opium) is confined to only a specialized cell system called the 'laticiferous system.' The genus *Papaver* is endowed with an articulated anastomosing structure of laticifers — the series of connected cells developed from single vertical files of parenchymatic cells resulting from the absorption of their end walls (Fairbairn and Kapoor 1960, Petri and Mihalik 1998) [12, 24]. They are distinguished from other cells by their large, irregularly shaped vesicles in the cytosol, constantly occurring in the vascular bundles' phloem tissue. The major latex protein (MLP) is deposited (Griffing and Nessler, 1989) [14].

Development of laticifers commences with chlorophyll formation even in the green cotyledonous foliage of the poppy plant. Since there is no latex trace when the cotyledons are still yellowish, axiomatically, latex-biosynthesis is concomitant with chlorophyll cells' development. Laticifers have been detected in sepals and ovaries (Fedde, 1936, Esau, 1977) [13, 10]; they are absent in seeds (ovules) and young seedlings before acquiring chlorophyll. The laticiferous system reaches the capsule (enlarged ovary) with the plant's growth from vegetative to reproductive phases. Latex (the raw opium) is biosynthesized and stored in vesicles in these laticifers. As the latex is a secondary metabolite (by-product) and probably of no use to the plant's survival, maintenance and growth, it is translocated mainly to its apex, i.e., capsule, for safe storage. Though latex is synthesized in and secreted from every plant organ (except petals and seeds), called 'source,' capsule commands a greater 'sink' capacity where the maximum concentration of latex is found. Thus, most latex moves through the laticifer tube from 'Source' to 'Sink,' which provides a safe locale for latex deposition in the poppy plant. The laticiferous system is pronounced and densely concentrated in the capsule's mesocarp region, making anastomose branching (Husain and Sharma 1983) [15]. The capsule thereby is the most convenient organ for the extraction of latex.

Thus**,** there are two major steps to ensure the harvesting of the gum or opium in opium poppy:

1) Proper and adequate biosynthesis of latex (opium) in the laticifers of ‘source’ organs
2) Efficient translocation of latex from the 'source' organs to the 'sink' (i.e., capsule).

These steps ought to be controlled by one or more gene(s) or gene systems.

Gum / Opium harvest from the opium poppy in India

The gum (latex) translocated from different plant organs to the terminal capsules is accumulated in ample amounts in the latter. This process begins right from the stage when the flowering primordia are formed at the rosette stage and continues till the greenish shade of the capsule. After about 15 days of petal-fall, it follows the capsule's hardening when valve traces reach their maximum density in the mesocarp (Fairbairn and Kapoor, 1960) [12]. This is the 'just right' stage (industrial maturity) of the capsule, ready for lancing.

Lancing

In India, it is a process of full-length longitudinal or circumferential cut/incision of the capsule, essentially in the sunny afternoon with a unique instrument or knife (called Nashtar or Nurnee or Naka). It identifies that the 'just right' stage of the capsule ready for lancing and the precise depth of incision are highly skilled jobs — the skill of workers acquired by experience over the years.

Latex/gum collection

The lancing causes oozing out of latex, transforming into a 'pellicle' facing the afternoon sun on the capsule's surface. The following day, it turns semi-solid when scrapped with a blunt-edged iron scoop (Setwa /Charpala), preferably before 9-10 AM (Fig.6). Generally, 4-6 cycles of lancing followed by collection are performed, which consume nearly a month. After that, seeds are harvested when the crop is thoroughly dried.

Thus, the whole operations of lancing-cum-collection of gum are tedious, time-consuming, and relatively costly components of opium poppy cultivation.

Storage and deposition of latex to Narcotics Department

The grower's daily collected fresh latex is placed into a wide-open iron or earthen container, weighed then, and adequately recorded in the 'daily produced register' maintained by the village *Lumberdar*. The stored stock of latex is churned and stirred daily to make it dry and homogenous. Excess water, if any, is further drained off — it is called *Pasewa*.

The whole amount of latex collected over all the lancings is

finally deposited (along with *Pasewa*) with the District Opium Officer (DO) in the Weighment Camp held by Narcotics Department at a specified place and time. Generally, 1-1.5 months after the lancing and gum collection operation is over in the area. The quantity of produce deposited by each grower is recorded, and its quality (purity) is then adjudged through 'touch and see' by the Camp Officials. All latex of the uniform quality is transferred into one bag or pot. A small sample from each such bag of different quality is then drawn in a Petri dish for oven-drying and determining the solid matter (or the moisture content) in the opium (latex). Accordingly, the 70º consistency (a standard state) of opium is calculated as per the following formula (Sharma *et al.*, 2002a,b) [28, 29]:

70º consistency = Solid wt. of opium × 1.4286

The total quantity of latex (raw opium) of adjudged purity deposited by each grower to the DO is now converted into 70º opium produced per hectare. This form is the basis of payment to the growers @ Rs.3000.00 to Rs.3500.00 per kg from 44 to > 100 kg/ha yield of latex deposited with DO.

Finally, the DO translocates lots of farmers' produce (opium) collected at Weighment Camps to the Chief Opium Chemist, Govt. Opium and Alkaloid Works, Ghazipur (Uttar Pradesh) and Neemuch (Madhya Pradesh) for chemical determination of morphine strength (MS – A, B, C, D grades) of each lot and then transferring them to appropriate storage vats (called 'godown) as per their MS for further grading and processing, etc. If any, the respective growers are then paid back the balance amount based on MS grades in the next Settlement Camp, where new licenses are issued or old ones renewed after careful consideration and scrutiny.

Thus, not only are lancing and gum collection cumbersome and expensive tasks at the farmer level, but also issuing licenses, determining purity, consistency, and morphine strength, as well as transportation and proper storage of latex in 'godowns' are somewhat more challenging tasks at the Narcotics Department level.

Opium poppy – An ancient medicinal and food plant

Perhaps no medicinal plant on record possesses so rich a food value and an excellent pharmaceutical property as does the opium poppy (Sharma *et al.* 1999a, b) [27, 30]. The opium poppy has been known and widely utilized by the human race as a medicinal and food plant since time immemorial.

Historical perspectives of opium poppy cultivation

Poppy seems to be one of the few species utilized, even cultivated, during pre-historic times (Bernáth, 1998) [4]. It has contributed to some major world civilizations (e.g., Egyptian 1555 BC, Greek 1500-1000 BC, Mesopotamia 700 BC) by having a considerable impact on socio-cultural developments. Ancient Sumerians (now in Iraq) called it *hul Gil*, i.e., the 'joy plant,' and used its seeds as food (Sharma and Singh 1983). Its 'sleep-inducing property was well known to Greeks since the 6th century BC. Greeks coined the word *opium* for the poppy head's juice, which remains in its place till today. They consecrated the poppy to several Gods and Deities, *viz*. the *Nyx* – 'Goddess of Night,' the *Morpheus* – 'Son of Hypnos,' i.e., God of dreams, and the *Thanatos* – 'God of Death'. In Egypt, opium was called *spnn spnn*, which relates to its sleep-inducing quality; hence, Egyptians revered the plant (1555 BC). Arabs called it *Abou-el-noun*, i.e., the 'Father of Sleep', and cultivated opium poppy throughout the Arab Empire during the 7th century AD. Chinese acquired the medicinal uses of opium from Arab traders in the 13th century AD.

There was no record of opium in India before the invasion of Alexander the Great in the 4th century BC, when Persians brought it for the need for their army (Bernáth, 1999) [5]. But it is still unclear who brought the poppy seeds to India for cultivation? Ritter cf. Veselovskaya 1976) [41] opined that Mongols were introduced in the 13th century when they conducted India's short raid. But Veselovakaya (1976) suggested long-ruling Arabs who introduced poppy plants in India for cultivation during the 7th century. The latter's contention is also borne out because the earliest description of poppy in Indian literature is already available before the 13th century in *Dhanwantari Nighantu* ca.1000 AD and its medical preparations *Shodal Gadanigraha* ca.1200 AD. (Sharma, *et al*., 2002a, b) [35, 36]. This means the cultivation of opium poppy was well established by the 16th century in the peninsular Malwa region of Madhya Pradesh. During Moghal rules, opium was a valuable trade item with China and other countries in the 15th century (Kohli, 1996) [16]. From the second half of the 18th century until independence, the British Govt. controlled the production, processing, and sale of opium in India. In April 1950, Govt. of India established 'The Narcotics Commission,' which rationalized and unified the control system on poppy cultivation (Kohli, 1996.) [16]. The entire area of poppy cultivation in Uttar Pradesh, Madhya Pradesh, and Rajasthan states is well monitored, and strictly ordained by Narcotics Department, Govt. of India.

The opium poppy has been legitimately cultivated for opium extraction in India, China, Egypt, France, Holland, Hungary, Poland, Switzerland, Greece, Spain, Portugal, Italy, Turkey, Romania, Australia, erstwhile USSR, Yugoslavia, Japan, Bulgaria, Iran, and Pakistan. But Turkey stopped opium extraction in 1972, USSR and Yugoslavia in 1973, and Iran and Pakistan in 1979. Later on, all other countries except India followed suit (Husain and Sharma 1983) [15]. Thus, barring India, no other country is now cultivating opium poppy for opium — India holds, by and large, the monopoly of opium production. Other countries have not completely abandoned poppy farming; instead, under the aegis of the United Nations' International Narcotic Control Board (INCB), their focus has changed from gum (opium/latex) harvest to direct extraction of alkaloids from poppy straw (capsule hulls). Some countries, such as Germany, Austria, Czech, Slovak, Hungary, Switzerland, Netherlands, Poland, Romania, Turkey, etc., only grow opium poppy for edible seeds and poppy oil. The biotypes or varieties used for opium production (gum collection) are GH varieties. Those used to extract alkaloids from the straw directly are CPS (concentrated poppy straw) varieties of the opium poppy.

In addition to the legal cultivation of opium poppy in the above countries, some countries have practiced illicit cultivation, exceptionally to provide the grist for the 'drug' industry worldwide. Two hotspots are known where such illegal cultivation is rampant. They are nicknamed 'Golden Triangle' (comprising adjoining regions of Thailand, Myanmar, and Laos) in Southeast Asia and 'Golden Crescent' (Iran, Afghanistan, and Pakistan) in South-West Asia. Their role in drug trafficking for opium abuse has grown beyond proportion threatening the human world over.

A remarkable medicinal and food plant

Since time immemorial, the opium poppy has been known for its medicinal properties conferred by the opium that it produces. The word 'opium' is derived from the Greek word 'Opos,' meaning juice (Bernáth, 1998) [4]. Opium has many

forms of application, such as pipe smoking, powder, capsules, tablets, juice, and tincture (laudanum) to treat sickness, pain, headache, diarrhea, cough, and diseases of eyes, earache, etc. (Sharma *et al*., 1988). Opium is also taken to offset extreme sorrow, insomnia, and anxiety. In former times, it was used to alleviate the excessively crying children. In *Sarangdhar Samhita* (1400 AD), its use is also prescribed as an aphrodisiac to tone up the sexual debility.

The above-stated effects of opium are consummated by its three main alkaloid components, *viz*. morphine, codeine, and papaverine. Morphine exerts depression and stimulation in the CNS and gut, simultaneously causing sedation and euphoria (Nyman and Hall, 1976; Thakur, 1983) [21, 40]. It is a strong analgesic – potent and suppressive in almost all acute pains such as cancer, kidney stones, or pancreatitis, where other analgesics fail. Morphine is also used in preparations to control typhoid fever, internal haemorrhages, traumatic shocks, dyspepsea, diarrhoea, and pulmonary edema combined with atropine in neural and intestinal colic and coronary cases thrombosis. Owing to these diversified medicinal uses and great difficulty in synthesizing its chemical substitute, morphine is considered a unique chemical compound of remarkable therapeutic value in modern medicine. Codeine is a less potent analgesic but a strong respiratory / cough depressant (antitussive) and smooth muscle stimulant. At the same time, papaverine exhibits a powerful anti-spasmodic effect on blood vessels and abdominal viscera. It is also prescribed to relieve gastric and intestinal spasms and asthma attacks. Synthetic papaverine is very cheap and widely used.

In addition to its medicinal uses, the opium poppy plant is also a valuable source of edible seeds and seed oil. The food value of its seeds was also known since pre-historic times as established by archeological excavations of lake dwellings in Switzerland, Poland, Netherlands, etc. from the earliest (before 4000 BC) to the middle and late Neolithic (before 2500 BC) periods (Nyman and Hall, 1976; Veselovskaya, 1976) [21, 41]. The ancient Sumerians (now in Iraq) used poppy seeds as food (4000 BC). Poppy seeds are widely used in the food industry – bakery, confectionery, spices, etc., because of their highly nutritious nature from high protein and oil contents. The poppy seed oil is also beneficial as cooking media for human consumption and valuable constituents for paints, varnishes, and soaps.

Opium poppy: The mystic 'joy plant.'

The opium poppy is not only a remarkable medicinal-cum-food plant; its historical and contemporary importance, coupled with its notoriety and mystique, can be attributed to very few plants (Facchini and de Luca, 2008). Its sleep-inducing property was well known to Greeks since the 6th century BC (Veselovkaya, 1976). They coined the word 'opium,' which causes, now we know, sleep. The Greeks extracted opium poppy plants to obtain a pain-killing drink named *meconium*. Hippocrates (460-377 BC) called this drink *poppy wine* and described it as a hypnotic, narcotic, styptic, and catharic agent (cf. Bernáth 1998) [4]. In Iraq, the ancient Sumerians (dating 4000 BC called it *hul gil* – the 'Joy plant. 'According to Fluckiger (Veselovskaya, 1976) [41], the use of opium as a narcotic was first started in Syria, where it was eaten and added to sweets and spices. Arabs used to call opium poppy *Abou-el-noum*, meaning 'father of sleep' (Nyman and Hall, 1976; Sharma *et al*., 1999) [21, 34]. The opium poppy and opium knowledge was prevalent in ancient Mesopotamia and Egypt. In *Assyrian Herbal* and the *Eber's Popyrus* dating 1555 BC, the opium poppy was known as *Spun-spun*. It was used as sleep-inducing medicine to pacify children from excessive crying (Nyman and Hall, 1976; Sharma *et al*., 1986) [21].

Opium was traditionally used in India extensively as a narcotic and a medicine. The Mughals, for example, used it as *tariayak* or in majun – the ladies would take it under the Urdu-euphemism of *Chunni Begham* (Sharma *et al*., 1999; Bajpai *et al*., 1996) [34, 3]. From the very early times, there were three preparations of opium: (i) *Afim*, (ii) *Madak*, and (iii) *Chandu*. The *Afim* is raw opium, while the other two were processed through recurrent washing and filtration followed by slow heating to obtain a product called *Kimam*, the base for *Madak* and *Chandu* both (Sharma *et al*., 1999; Lal *et al*., 2011) [34, 17]. The *Kimam* mixed with an equal quantity of *Jesu* (a semi-solid mixture of guava and beetle leaves boiled in water, filtered, and fried on slow fire) results in *Madak* being made into pills. A small part of this is smoked through the huble-bubble pipe (*Hukkah*) for 'joy.' The *Chandu* is prepared by mixing the half-burnt ashes of both *Madak* and *Kimam* in equal measures and then smoked by a special long pipe with brass or tin bowl at the far end (Sharma *et al*., 1999) [34]. However, both *Madak* and *Chandu* are now obsolete.

In addition to the opium and its products *per se*, there has been frequent powder of poppy capsules mixed in tea – known as *Bonda* tea in local jargon in Punjab, J & K, etc., among heavy lorry drivers and bonded laborers. The capsule powder contains a fraction of opium alkaloids that intoxicate drivers and laborers who work more than customarily. Thus, this 'joy plant' of ancient Sumerians occupies a prominent place even today in society. The 'joy' from opium poppy emanates essentially from the opium and opium alkaloids that it contains. The opium and its components, especially the three morphine alkaloids, *viz*. morphine, codeine, and thebaine, are the natural (authentic) narcotics – generally referred to as 'opiates.' They possess narcotic property, which produces insensibility or stupor because of their depressant effects on the CNS (Central Nervous System), thereby reducing pain and inducing sleep. The word 'narcotics' comes from the Greek work *narkotikos*, which means benumbing the senses. Therefore narcotics (opiates) are frequently used to kill severe/acute pains. But excessive and regular use of these narcotics leads to drug dependence and associated syndrome (Nielsen *et al*., 1983) [20]. Drug addiction (dependency) results in misuse/abuse of narcotics, which has tremendous ramifications at social, economic, political, and other levels.

Opium-linked Global Abuses

The deadly derivatives of opium, morphine, or the notorious heroin, have played havoc with society's younger population. International terrorism, which thrives most on its arms and weaponry, procured through the illegal narcotics trade, has grown by leaps and bounds (Sharma *et al*., 1999) [34].

Consequences and control Measures

After 156 years, Hong Kong was reinstated to China on June 30, 1997. Britain annexed it through a 'Treaty of Nanging.' In 1839, an administrator of China's emperor stopped the illegal trade of opium in China by European businessmen for public consumption. It burnt 1500 metric tons of opium, inflicting great harm to European countries' business interests, especially Britain. Great Britain knows a brawl between a British sailor and a Chinese native assaulting a blow to the western prestige and profits resulted in the famous 'Opium War' (1840-42) thrust upon China. The war continues, and it

continues now even on a broader scale in different forms, across the countries, continents, and the world. It was an opium trade; now, it is the menacing drug trafficking — illegal drug trade, which has engulfed the new generation world.

Global opium abuses and consequences

Opium abuses

Owing to its sleep-inducing and intoxicating property and rendering a blissful 'Kick,' illicit cultivation of opium poppy and illegal use of opium have been perpetuated as social evil for centuries (Husain and Sharma, 1983) [15]. With the easy chemical conversion of morphine into a 5-fold more potent narcotic compound – the notorious heroin – the opium-linked abuses have now assumed a menacing proportion worldwide. More than 17 million world peoples are opium addicts, and nearly half as much to heroin this time around. About 2 m people are opium addicts in India. In 1971, about 200,000 to 300,000 heroin addicts were recorded in the USA – an alternative figure suggested 30,000 opiate addicts in New York alone, where heroin addiction was the major cause of death among males 18-35 years of age (Husain and Sharma, 1983) [15]. Multiple surveys have indicated that many high school students have had experience with contraband drugs by completing their graduation. As per other authoritative estimates, more than 500,000 heroin dependents are roaming in America – 25% of these are teenagers. All levels of the American community are afflicted with this 'white death' trap.

But, it is not only America; this menace has spread horizontally with pandemic virulence. In the U.K., the number of opiate addicts recorded in 1961 was only 470, which rose to nearly 1200 in 1971. It has captured an unknown number of victims into its tentacles. According to a recent United Nations Drug Control Program (UNDCP) report, only 30,000 heroin addicts were recorded in Pakistan a decade ago. Now it stands ≈1600,000 (51% of 3 million).

Similarly, in India, till 1975-76, heroin addiction was not on record. But two decades later, the number surged to about 2 million (2% of the whole population), including 35% college students. China is another country where opium addiction is much prevalent, though the Chinese government has time and again banned its use.

Consequences of Opium Abuses

The uncontrolled and non-medicinal use of opium, morphine, and heroin has several devastating consequences. The following three, which are largely interdependent and intertwined, are the most serious:

Health hazards and confidence erosion

Opium and opiates are mixed blessings. They are used as a medicine against cough and diarrhea reduce pain and induce sleep. But in large quantities, they are dangerous, but they also develop drug dependence. On cut off the drug's supply, the latter quality causes characteristic symptoms of withdrawal as described in the book ‘The Opium Poppy’ by Husain and Sharma, (1983) [15] including restlessness, irritability, shivering, muscular tremors or convulsions, headache, sneezing and crying, flushing of the skin (cold turkey), chills, mydriasis, insomnia, abdominal cramps, dilated pupils, excessive sweating, derilium, loss of appetite, vomiting, diarrhoea (leading to dehydration and weight loss), and finally a sense of desperation and an obsessing desire to secure a 'fix' either by theft or crime. These symptoms increase in intensity for up to three days and gradually diminish over 5-10 days. However, weakness, insomnia, nervousness, and muscle pain may persist for several weeks. Hallucinations and delusions can also develop, which are usually terrifying. In extreme cases, it may prove to be fatal. Thus, misuse of opium and its products, namely morphine and heroin, cripples individuals and society's personality and confidence.

Drug-trafficking and Parallel Economy

Drug trafficking has created a parallel economy of — around the US $ 100 billion based on drugs is annually involved in the world economy. The business of drug trafficking started 125 years ago as a small-scale industry. Now it is very well organized international trade. In the USA and Canada, the demand for drugs per man is the highest — the amount involved is more than the total GDP of 80 developing countries. It can be gauged with heroin, which sells in the contraband market @ 3500 to 5000 US $ per kilogram. According to UNDCP reports, its share is 8% in the international market. As per International Monetary Fund (IMF), 2% of the world economy is based on the illegal drug trade. The enormous illicit profits generated by the drug syndicates are used in the black economy. In the past, most opium produced in South-East Asia, i.e., 'Golden Triangle,' was refined into heroin in laboratories along the Thai-Myanmar border and then coursed through Thailand and Hong Kong for transit to western markets. Currently, southern China and Taiwan are fast becoming new transit routes to transport heroin and opiates to lucrative markets in other parts of the world. Myanmar alone is the source of the bulk heroin sold in the USA. On the other hand, about 75% of the heroin seized in the European market originates from South-West Asia, i.e., 'Golden Crescent. Most of the heroin is transported overland via Turkey, Bulgaria, and Hungary, via the Balkan route through India.

As per a recent UNDCP report, till 1980, the 'Golden Triangle' produced hundreds of tons of heroin and catered to the USA and Europe's demands by supplying heroin with around 700 tons per year. However, at the end of 1979, when the supply from the 'Golden Triangle' shrunk, 'Golden Crescent' became most active. Afghanistan and Iran are registered as the biggest producer of opium. But political upheavals in Iran and Afghanistan during 1980 led to substantiate fall in their opium production. Pakistan took advantage, and its illicit production of opium and heroin then jumped relatively high. The laboratories for refining opium into heroin are located in the lawless tribal belt along the Pak-Afghan border, where some of Pakistan's most notorious drug barons live safely. According to a recent book, *Drugs, Youth and Society*, comprising 14 contributions from eminent personalities and edited by Dr. M.C. Paul of Jawaharlal Nehru University (JNU), New Delhi, Pakistan, today produces around 80 tons of heroin per annum and is widely getting recognized as the 'Kingdom of heroin.' The bulk of its raw material (i.e., opium) comes from Afghanistan, which produces about 2000-4000 tons of opium per annum (Antonio Maria Costa, 2007).

India is surrounded by the 'Golden Triangle' in the east and the 'Golden Crescent in the west. Not surprisingly, therefore, it often serves as a conduit for opium and heroin trafficking – a transit passage of the international chain of drug smuggling. However, till 2020, India was nowhere in international drug trafficking. Since India now holds the monopoly of opium production globally, it also creates a potential local market of consumers. This has rendered about one million people heroin

addicts and two million opium addicts in India, according to the book, Drugs, Youth and Society.

Global narco-terrorism

In the recent past, the spectra of terrorism have engulfed the whole world, both within and across national boundaries. Most sophisticated weapons and maintenance, training and transport, etc., of spoilt men and woman folks, receive finances from illicit drug trafficking. For instance, the drug barons are financing the separatists in India's Kashmir, Punjab, and North-East region. The major part of Punjab terrorism, it is said, is linked to drugs. Pakistan drug Mafia supports Khalistan movements in India. They are also financing the pro-Inter-services Intelligence (ISI) Afghan groups in Afghanistan. Recent turmoil in Kagestan, Afghanisthan, Chechnya, and India (Kargil conflict) largely by the Taliban is another case in point. Blowing the American Embassies in Kenya and Tanzania is a dangerous example of drug-based terrorism. The threat to international peace and relationship has recently grown to a new high where the world's two biggest democracies — United States of America and India.

Drug-based terrorism within a country, city, or society is also no less rampant in the USA, UK, Europe, Africa, and several other countries. This is terrifying. Free use of weapons among drug Mafias to promote their illicit trade or transaction of heroin or other drugs is not rare. Criminality within the family is a common hazard or danger of drug addiction. This may occur in terms of theft or prostitution. Heroin users' social relationship is significantly at stake. In short, the money generated from drug trafficking (the profit "down the line" is over 5,000% of the original cost) is said to be mostly used in political manipulations and elections, bureaucratic corruption, building up of parallel power centers, extravagant lifestyles of a few, investment in real estates, the assassination of opponents, group rivalries and support of national and international terrorism. These are all in addition to crippling the youth and weakening the social fabric.

Control measures: Approaches to tackling global opium-abuses

The specter of opium-linked abuses has been haunting humankind for centuries. The current trend is dangerously upbeat. The precious lives of opium/heroin addicts hang in the balance. The fate of our future generation and the nation with internal and international terrorism staring at the face is seemingly sealed. Several administrative and punitive measures were taken to combat this problem.

Administrative/legal control measures

For the first time, anti-opium ordinances were enacted to contain the evil of opium, e.g., in the United States in 1875 in San Francisco. In 1882, the New York State Assembly passed a bill against New York City's China Town, where opium dens flourished. The Federal Bureau of Narcotics (FBN) was established in 1930 in the USA. Before that, the first international effort was made by establishing an International Opium Commission in Shanghai in February 1909, followed by its quick conventions in the Netherlands in 1912, 1913, and 1914 for tighter international control. After World War I, the League of Nations took over the charge in 1921. The advisory committee on the traffic of opium first met in 1921, followed by Geneva Conventions in 1925 and 1931. After World War II, United Nations Organization (UNO) was created, which adopted a Narcotic Protocol in 1948 under the World Health Organization (WHO). Subsequently, the International Narcotic Control Board (INCB) and the United Nations Drug Control Programme (UNDCP) of UNO became responsible for controlling opium-growing countries and international drug trafficking.

Similarly, in India, a series of measures have been taken by the Government of India, including plugging leakage from the stockpile, strengthening and revamping the enforcement arrangements, deterrent punishment under the new legislation, and effective systems of control under the auspices of the Central Bureau of Narcotics (CBN). According to official sources, while the diversion of opium from licit cultivation is minimal — the minimal seepage gets consumed within the country; there is virtually no pilferage from opium stocks and no out-smuggling abroad. More than 75% of the heroin seized in India comes across the Indo-Pak border, only around 0.37% from South-East Asia. Enforcement agencies have intensified their activities at the land border, airports, and other vulnerable areas.

Indeed this problem cannot and will not be solved by stringent enforcement of drug legislation or further punitive penalties for drug misuses alone, as has been followed for centuries. Chasing the 'merchants of death' trafficking the heroin ("Smack, Scag, Shit, junk, hard stuff") or other opiates across the world could not solve the problem either. Indeed, all physical and legislative measures adopted have not eradicated opium-linked social evil.

Biological control measures

Despite all legislative punitive measures, the drug-trafficking has not been contained in the world. Instead, it is growing unabatedly. This attracted Biologists' attention to develop specific biological measures to arrest the pace of opium abuse in society. Following are the major biological approaches that have been deployed for this purpose:

Crop substitution

Replacing the opium poppy with some equally remunerative alternate crop under cultivation is a viable proposition to stop opium production, hence no abuse. A sister species, *P. bracteatum* is a potential alternative to *P. somniferum*. It produces only thebaine and no morphine at all. The former is a precursor for easy chemical conversion to codeine and several narcotic antagonists, like naloxone, naltrexone, and Bentley compounds. During the 1970s, serious attempts were made to domesticate and cultivate *P. bracteatum* as an alternative source to *P. somniferum* for codeine production. However, its cultivation is confined to temperate zones; it fails to produce seeds in sub-tropical countries.

In the Philippines, the opium poppy has been sought to be replaced by *Chrysanthemum morifolium* for herbal tea. Besides, the cultivation of German Chamomile, psyllium, rose-scented geranium, etc., could be equally remunerative (Sharma *et al*. 1999a, b) [27, 30].

Development of 'Silver Bullets'

Another biological measure is the approval of a $ 23-million anti-drug program by the U.S. Congress to develop "Silver Bullets,"— the plant pathogen for killing all the narcotics-producing plants, including opium poppy. However, this has run through rough weather because this biowar against drugs militates with Article 1 of the 1972 Biological and Toxin Weapons Convention (BTWC), hence abandoned, by and large. Nevertheless, a silver lining showed amidst the dark cloud: genetic manipulation on a war footing of the very

source of the opium, i.e., the opium poppy plant, by converting it into a nonnarcotic plant.

CPS cultivation

Opium alkaloids (mainly morphine, codeine, and thebaine) are also present in poppy straw (generally the capsule hull + 1/3 of peduncle /stalk) and opium. But they occur infractions – only morphine may be above 1.0% as in var. *We developed Sanchita* (1.0-1.2%) at CSIR-CIMAP (Bajpai *et al*. 1996, CIMAP, 1993) [3]. In Tasmanian varieties (Australia), the average morphine content in straw varies from 0.6 to 0.8%. Nielsen *et al*. (1983) [20] had made a breakthrough by developing triple-cross hybrids where new selections had morphine as high as 2.3%, with the average at 1.3 to 1.6%. But the, further report on their performance is not available in the literature. This morphine (but not other alkaloids) with a shallow concentration in the straw is solvent extracted directly from the poppy-straw powder. The filtrate is then again subjected to re-extractions so that the strength of morphine is enhanced at 50-80% in the final concentrate of poppy straw (CPS). The CPS varieties, which possess more morphine in the poppy straw, can thus be cultivated to obtain morphine directly from a straw rather than from the gum/latex (opium). Thereby latex collection is completely avoided to minimize any social risk of opium.

Based on this premise, nearly all the poppy-growing countries except India have shifted their emphasis from gum gathering to straw harvesting through CPS cultivation under the International Narcotics Control Board (INCB). However, the CPS cultivars are not free from opium; hence, the danger looms large. It is only a partial treatment of malice of opium abuse.

Development and deployment of *true* CPS cultivars

The *true* CPS varieties do not synthesize latex (opium) but have a high concentration of opium alkaloids (morphine/codeine/thebaine) in their capsule hulls (straw). Thereby, opium abuse may be substantially arrested. Such cultivars would retain the medicinal value of opium poppy (as vital alkaloids are available) without the risk of opium-linked abuses — no opium, no abuse. Yet, there is a dim possibility of misutilization of morphine directly extracted from poppy straw, though this will be a costly dam affair, good enough to discourage such activities. Therefore, the development of *true* CPS cultivars is the most pragmatic and possibly better solution to opium abuses without sacrificing the pharmaceutical value of major alkaloids present in the straw. However, for the complete eradication of opium-linked global abuses, the development of entirely nonnarcotic (opium less and alkaloid-free) cultivars is the real choice.

After evolving a CPS var. – *Sanchita*, we vested in a serious attempt to develop a *true* CPS cultivar not to be caught napping when INCB invokes replacing gum poppy (GH varieties) with CPS cultivars in India. Adopting *true* CPS cultivars rather than the current CPS varieties under cultivation would be better. Significant advances have been made in developing *true* CPS cultivars at CSIR-CIMAP, Lucknow (India)'.

Fig 1: Morphological Variability in opium poppy

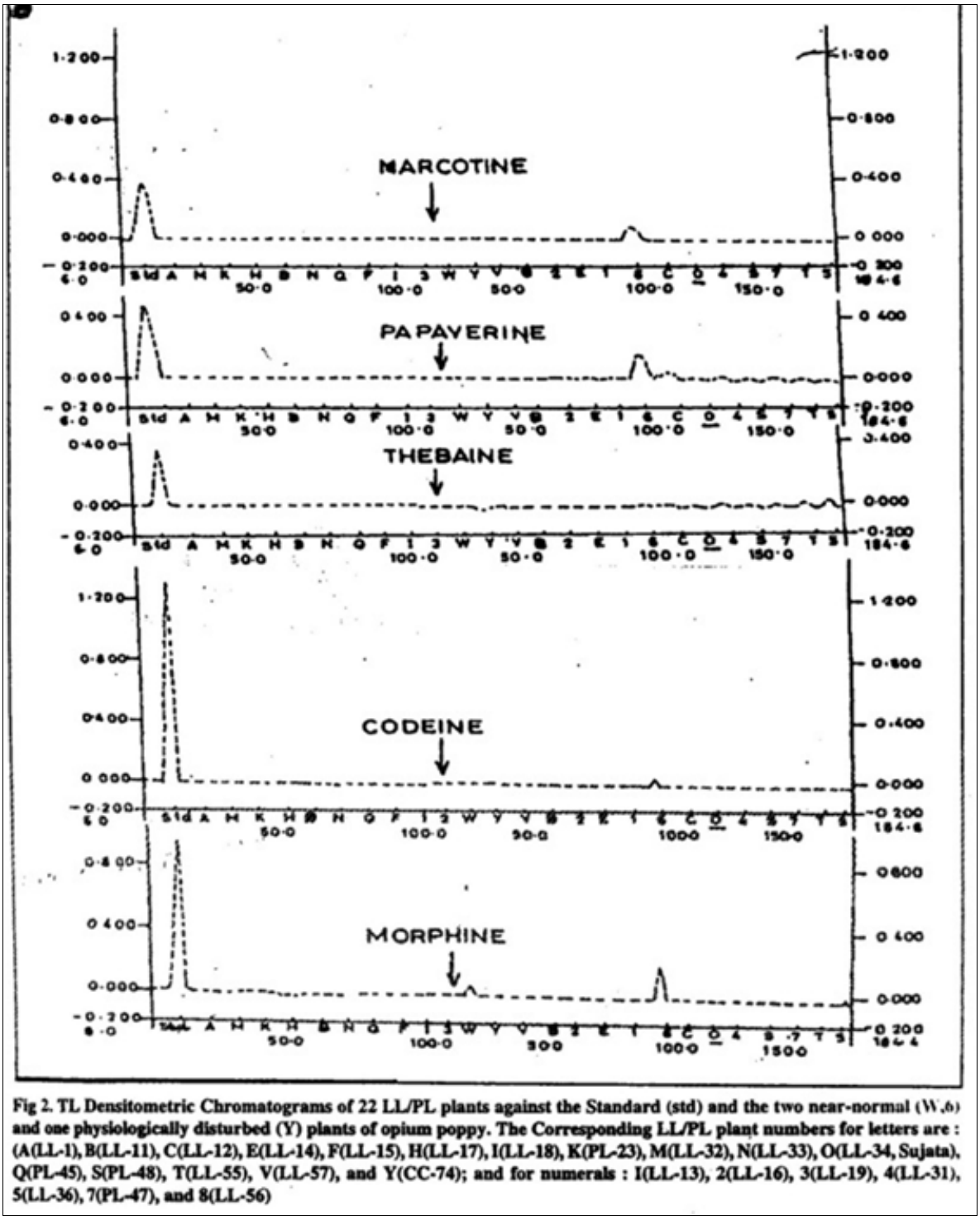

Fig 2. TL Densitometric Chromatograms of 22 LL/PL plants against the Standard (std) and the two near-normal (W,6) and one physiologically disturbed (Y) plants of opium poppy. The Corresponding LL/PL plant numbers for letters are : (A(LL-1), B(LL-11), C(LL-12), E(LL-14), F(LL-15), H(LL-17), I(LL-18), K(PL-23), M(LL-32), N(LL-33), O(LL-34, Sujata), Q(PL-45), S(PL-48), T(LL-55), V(LL-57), and Y(CC-74); and for numerals : I(LL-13), 2(LL-16), 3(LL-19), 4(LL-31), 5(LL-36), 7(PL-47), and 8(LL-56)

Fig 3 (a-f): a. Parent latex variety Sampada b. partial latex mutant c. latex less mutant, seeds of mutants, latexless variety Sujata and Dr-44 d. black seeds of opium poppy

Manipulating opium and alkaloids biosynthesis through mutation breeding

Perhaps the last approach to contain the global menace of opium abuses is the genetic conversion of narcotic 'opium poppy' (with both opium and straw alkaloids) into non-narcotic (opium less and alkaloid-free) 'seed poppy.' Half a decade ago, the author and his team became unlikely volunteers in the crusade against narcotics. While law-enforcement agencies worldwide chased drug traffickers with guns, they armed themselves with physical and chemical mutagens and struck at the major root of the opium menace, i.e., *Papaver somniferum*, the opium poppy plant — source of opium and heroin. Thus, we have eventually broken the poppy's spell. In its applied form (Plant Breeding), genetics has been the prime pusher of the 'Green Revolution' by evolving fertilizer responsive and lodging resistant dwarf

varieties, especially rice and wheat, during the mid-1960s in India and other countries. The author and his researchers' team could recently perform similar feats in the opium poppy, *albeit* for a negative change, i.e., producing opium less opium poppy through mutagenesis. In other words, we have been able to arrest the biosynthesis of latex and straw alkaloids in the opium poppy plant by subjecting it to the bombardment of gamma rays coupled with ethyl methanesulfonate (EMS) treatment. Subsequent testing and evaluation of mutant progenies culminated in the development of many opium-less and alkaloid-free genotypes. Such genotypes are naturally a cheap and permanent means of combating opium-linked global abuses if brought under cultivation. They are rich sources of high-value poppy seeds (*khas-khas*). Detailed discussion on mutation breeding on opium poppy occurs as follows:

Recessive Loci Pps-1 and OM Differentially Regulate PISTILLATA-1 and APETALA3-1
Expression for Sepal and Petal Development in Papaver somniferum (Sharad *et al*., 2014)

The involvement of PISTILLATA (PI) and APETALA (AP) transcription factors in the development of floral organs has previously been elucidated, but little is known about their upstream regulation. In this investigation, two novel mutants generated in *Papaver somniferum* were analyzed - one with partially petaloid sepals and another having sepaloid petals. Progeny from reciprocal crosses of respective mutant parent genotypes showed a good fit to the monogenic Mendelian inheritance model, indicating that the single, recessive nuclear genes likely control the mutant traits named "Pps-1" and "OM" in the partially petaloid sepal and sepaloid petal phenotypes, respectively. Both paralogs of PISTILLATA (PapsPI-1 and PapsPI-3) were obtained from the sepals and petals of *P. somniferum*. Ectopic expression of PapsPI-1 in tobacco resulted in a partially petaloid sepal phenotype at a low frequency. Upregulation of PapsPI-1 and PapsAP3-1 in the petal and the petal part of partially petaloid sepal mutant and down-regulation of the same in sepaloid petal mutant indicates a differential pattern of regulation for flowering-related genes in various whorls. Similarly, it was found that the recessive mutation OM in sepaloid petal mutant down-regulates PapsPI-1 and PapsAP3-1 transcripts (Singh *et al*., 2014). The recessive nature of the mutations was confirmed by the segregation ratios obtained in this analysis.

High alkaloid yielding big capsulated dominant mutant in opium poppy (*Papaver somniferum* L.)

The CSIR- Central Institute Medicinal and Aromatic Plants developed two high-yielding varieties: 'Shyama' and 'Shweta' through genetic selections in diverse local landraces. The farmers now cultivate these two varieties under the supervision of the Narcotics Department of the Government of India. In order to ensure further genetic improvement in opium poppy Scientists of CSIR-CIMAP, Lucknow undertook induced mutations on these two varieties, employing gamma rays (50, 150, 200 Gy) and EMS (0.2, 0.4, 0.6%) and combined treatment (50 Gy + 0.2% EMS, 50 Gy + 0.4% EMS, 50 Gy + 0.6% EMS). Inbred seeds raised from the two varieties were treated with these mutagens. As a result of extensive screening of treated populations over successive generations, 16 mutants were isolated (Chauhan *et al*., 1987; Chauhan *et al*., 1993) [8, 7]. Among these 16 induced mutants, a rare variant, big capsulated mutant (BC), was recovered in M from gamma-ray irradiated (50 Gy) material, which stood out as the best genotype for various morpho-physiological plant attributes, including total straw alkaloid content. The origin of BC has already been demonstrated and referred to as induced dominant mutation (Patra *et al*., 1990; Lal *et al*., 2013; Lal *et al*., 2014). High capsule number/plant, reduced capsule index (width/length), high straw biomass yield/plant, high seed yield/plant, and high morphine concentration in BC, distinctly marked it from the parent variety 'Shweta.' Mutants were raised using the bulked seeds from representative selfed plants in each generation. Evaluation of the mutant for different metric traits in the advanced M7 generation was performed based on records on 30 randomly selected plants. Productivity assessment trials were conducted on BC (M4-M7 generations) successively for four years (1988-92) to determine its economic viability. The yield data revealed that the mutant BC (designated as 'Vivek') is found to be highly superior to the control ('Shweta') as well as another high straw alkaloid yielding variety ('Sanchita') for both straw biomass and morphine yields. Per hectare, straw and morphine yields were 10-75 q and 11-35 kg, respectively, as against 7.70 q and 4.71 kg in 'Shweta' and 5.72 q and 5.38 kg in 'Sanchita.' Per hectare, seed yield of Vivek's was 14.80 q as against 9.8 q of the parental variety 'Shweta.' 'Vivek' has recently been released by the Institute for its commercial cultivation in subtropical belts of India (Anonymous, 1993). Since opium poppy is commercially cultivated for both alkaloids and seed yield, releasing the mutant variety 'Vivek' *is* likely to boost the commercial cultivation of Indian opium poppy.

Dwarf mutant of Papaver somniferum with high morphine content

Opium poppy, *Papaver somniferum* L. is an important medicinal plant known for its morphine, codeine, and thebaine alkaloids. CSIR-CIMAP, Lucknow had earlier released two latex opium yielding poppy varieties, "Shyama" and "Shweta," which are now cultivated by the farmers under the Narcotic Department's supervision Government of India. However, these varieties became susceptible to downy mildew (*Peronospora arborescens*). Lodging due to heavy capsule weight is another problem affecting latex yield. With these problems in mind, we undertook mutation breeding on the above mentioned two varieties employing gamma rays (5 kR, 15 kR, 20 kR) and EMS (0.2%, 0.4%, 0.6%) and combined mutagens (5 kR + 0.2% EMS, 5 kR + 0.4% EMS and 5 kR + 0.6% EMS). Mx from the treated seeds (405 plants) was raised in winter 1984-85. M2 generation of 13,500 plants (i.e., 270 M^ progenies x 50 plants) was raised in winter 1985/86. A dwarf mutant with high morphine content was identified in M2 from the variety > "Shweta" treated with 5 kR + 0.4% EMS. The mutant differs by its dwarf stature, compact leaf arrangements, multilocular capsules, increased capsule number, and small capsule size (Chauhan *et al*., 1987; Chauhan, 1989) [8, 6]. The mutant is under testing for its superior morphine production. It may be used as a dwarf gene source in hybridization for improving lodging resistance. This mutant is a novel type unavailable in our germplasm collection (Table 1).

Table 1: Alkaloid content and other traits of dwarf poppy mutant and its parent in M2. (Mean + SE based on 22 plants; alkaloid value based on 5 bulked samples in case of control and 15 samples in the mutant.)

S. No.	Characters	Dwarf mutant	Parent variety Shweta
1.	Plant height (cm)	~47.71 + 1.36	95.90 + 1.08
2.	Peduncle length (cm)	14.98+0.50	21.72+0.20
3.	No. of capsules/plant	8.77 + 0.85	2.54 + 0.11
4.	Capsule index	0.66 + 0.02	0.85 + 0.02
5.	Anther length (cm)	0.33 + 0.01	0.49 + 0.01
6.	Length of filament (cm)	1.33 + 0.03	1.52 + 0.02
7.	Straw weight (g)/plant	12.60 + 1.46	21.68 + 0.19
8.	Morphine content (%)	0.84 + 0.03	0.42 + 0.04
9.	Codeine content (%)	0.07 + 0.01	0.06 + 0.01
10.	Thebaine content (%)	0.07 + 0.01	0.06 + 0.01

(Chauhan *et al*., 1987) [8]

Inactivated or weakened biosynthesis of latex

A mutagenesis is a powerful tool for inhibiting enzyme function, which can weaken or prevent the formation of any secondary metabolite (Patra *et al*., 2002; Sharma *et al*., 2004). In opium poppy, the opium and opium-alkaloids, particularly the morphine (source of heroin), are addictively narcotic, leading to menacing global drug abuses. Their excellent medicinal value notwithstanding (Husain and Sharma, 1983; Sharma *et al*., 1999a b; Lal *et al*., 2011) [15, 27, 30, 17]. The genetic conversion of latex ‘opium poppy’ into latex less 'seed poppy' through mutation breeding resulted in opium less and very low alkaloids in straw mutant LL-34 (Variety Sujata). Variety Sujata has been developed through the extraordinary effort of mutation breeding, representing a genetic transformation of narcotic `opium poppy` into a non-narcotic `seed poppy.` Being opium-less and alkaloid-free, variety Sujata offers a cheap and permanent means of combating opium-like social abuses worldwide besides, as it is non-narcotic.

Variety Sujata (*Papaver somniferum* L.)

The mutant LL-34 is opium less (Figure 2), where latex biosynthesis peters out as the plant reach the lancing stage. The five primary opium alkaloids, morphine, codeine, thebaine, papaverine, and narcotine, have little or no effect on its straw (capsule hull). The plant is normal, and the seed yield was impressive (5.66 g per capsule and 13.5 kg/100 m^2 (8.5 q/ha). More importantly, seeds contain as high as 52-59% vegetable oil (much higher than most oil-seed crops) which is mainly unsaturated, i.e., suitable for dietary control of coronary heart disease and even diabetes arising from lipid abnormalities (Sharma *et al*., 1999a) [27]. The mutant LL 34, re-designated as variety Sujata, is a potential supplement to the production of edible seeds and seed oil and a cheap and permanent solution to abate opium-linked social abuses across the world (Sharma *et al*., 1999b; Sharma *et al*., 2002) [30].

Stability of variety Sujata

The var. Sujata was evaluated and confirmed for its non-narcotic nature (opium less and straw alkaloid-free) over three generations (M2, M3, and M4) under the northern sub-tropical conditions of Lucknow, Uttar Pradesh, where opium poppy ingrown in a large area. Hence, var. Sujata is stable for its qualitative trait of opium lessness. However, its quantitative traits, like seed yield and oil content, may vary due to genotype × environment interaction, as is common in all seed and oil drops. This mutant variety is also registered (by The Plant Registration Committee, ICAR, New Delhi) INGR No. 01045 (Figure 3).

Conclusion

Mutagenesis is a potent tool for preventing or weakening the synthesis of any secondary metabolite by decreasing enzyme performance. Despite their significant therapeutic utility, opium and opium-alkaloids, particularly morphine (source of heroin), are addictively narcotic, resulting in dangerous global drug misuse. In straw mutant variety Sujata, the genetic change of latex 'opium poppy' into latex less 'seed poppy' by mutation breeding resulted in opium less and very low alkaloids. Another issue affecting latex yield is lodging caused by excessive capsule weight. The above difficulty was also handled by creating a dwarf mutant of *Papaver somniferum* with a high morphine concentration by mutation breeding.

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Conflict of interest

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