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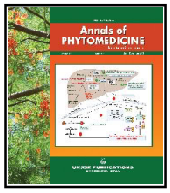

Review Article : Open Access

A comprehensive review on phytochemistry and pharmaceutical potential of opium poppy (*Papaver somniferum* L.)

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Abstract

Papaver somniferum L. is a self-pollinating, ancient angiosperm herbaceous annual, biennial, and short-lived perennial plant that is used for food, vegetables, oils, medicine, and ornament. The latex obtained from capsules contains nitrogen-containing secondary metabolites, which opium is a class of alkaloids with potent analgesic properties. The major alkaloids present in latex are morphine (15-20%), codeine (4-6%), thebaine (1-3%), narcotine (5-10%) and papaverine (0-2%).

Numerous solvent systems, including methanol, acetic acid, acetonitrile, ammonium acetate, and sodium acetate, are used in electrophoresis and chromatography procedures to quantify and isolate different alkaloids at predetermined pH levels. Important morphinane alkaloids belong to the group that works on the central nervous system (CNS) are highly addictive, analgesic (pain relief), and narcotic compounds. Other opium alkaloids like papaverine and narcotine relax muscles pain, while codeine has antitussive properties used as cough suppressants and anticancer activity. Thus, the article focused on the pharmacological and phytochemical aspects of opium poppy alkaloids.

1. Introduction

Plants are the primary source of food, energy, and medicine serves the entire world population. The majority of the plant species are angiosperms that consist of around 13, 000 genera and 250,000 to 300,000 species, thus covering around 80% of the entire plant kingdom (Monish *et al.,* 2022). These remarkable numbers of diverse plant groups are used for several purposes, such as fruits, crops, ornaments, and agricultural and medicinal herbs. Due to the creation of incredibly powerful drugs, frequently used in therapeutic applications (Srinivasan and Murali, 2022). The benefits obtained from plants are due to various primary or secondary metabolic activities. The first activity are essential components for plant growth and are synthesized constitutively throughout the life cycle, and second usually responsible for protecting the plant against biotic and abiotic stresses and less toxic against human responses (Chen *et al.,* 2016; Arif *et al.,* 2022).

Opium poppy (*P. somniferum*), which belongs to the dicot family Papaveraceae, is an annual short-lived herbaceous self-pollinated angiosperm that grows in a temperate climate and is native to the Eastern Mediterranean region. However, due to extensive cultivation and introduction of the plant throughout the European countries prevailing suitable climatic conditions, the origin of the species is still uncleared and obscured (Nigam *et al.,* 1989; Singh *et al.,* 1998). This species found across the old world, from subtropical to temperate areas, and from the 60° northwest Soviet Union to tropical areas in the south. On the other hand, recent climate change has become one of the critical drivers of shifts in plant species geographical distributions (Mishra *et al.,* 2013) (Figure 1). Legally, cultivated areas of Asian and European countries such as India, China, Japan, Yugoslavia, Poland, Germany, Netherlands, Argentina, Spain, Hungary, and Egypt (Pushpangdan *et al.,* 2012; Verma *et al.,* 2015). Opium poppy is used for food, vegetables, oil, medicine, or decorative purpose (Mishra *et al.,* 2013). Poppy seeds are ripened and dried for extracting seed oil used as an ingredient in many food items because they are non-narcotic (Singh *et al.,* 1995). Seeds of opium poppy are small white/black kidney-shaped and rich source of oils (45-50%), protein (24%), various minerals such as iodine, zinc, copper, manganese, magnesium, and are primarily used in bakery products for human consumption. All the important narcotic drugs found in the plant as latex form of unripe capsule (Azcan *et al.,* 2004; Özcan and Atalay, 2006; Carlin *et al.,* 2020). The latex is bitter, pungent odour, and its colour varies depending on the type of opium poppy cultivar (Martindale, the extra pharmacopoeia, 1989). For example, the opium of Turkish varieties is chocolate brown, while Indian varieties have dark brown coloured latex (Mishra *et al.,* 2013). The latex of opium poppy comprises of several alkaloids along with a diverse mixture of chemical compounds such as resin, wax, sugar moieties, fat, rubber, salts (*e.g.,* sulphate) (Mishra *et al.,* 2013). The alkaloids of opium poppy contribute to a valuable resource for therapeutic development as it is one of the richest sources of a diverse array. One such metabolite is benzylisoquinoline alkaloid

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(BIAs) which possesses immense medicinal importance (Jablonicka *et al.,* 2018). BIA comprises more than 2500 compounds, including five major alkaloids, *i.e.,* morphine, codeine, thebaine, papaverine, and narcotine. Opium latex contains a large amount of these alkaloids (Frick *et al.,* 2005; Mishra *et al.,* 2010). These compounds are widely used in modern medication systems as an analgesic, cough suppressant, and pharmacologic protrusive therapy.

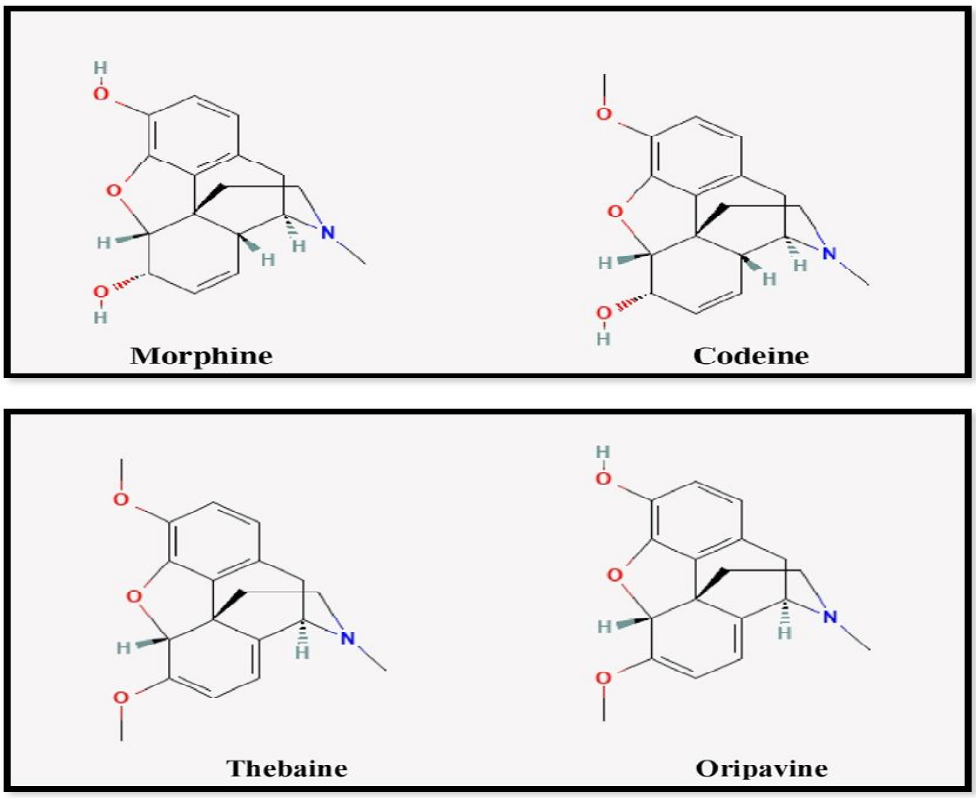
Figure 1: Opium poppy field view in CSIR-NBRI, Lucknow.

2. Phytochemical compositions

Natural products (NPs) derived from plants, or phytochemicals, have grown in significance as therapeutic molecules because they have a wide variety of metabolites (Warrier, 2021). In opium poppy alkaloid was originally used for the substances that react with the acids to form the salts like the inorganic alkalis. It contains various numbers of compounds which are influenced by the amount of amino acid used as nitrogen source (Facchini, 2001). Starch, tannin, oxalic acid and fat are also found as common constituents in alkaloids, thus resulting in adulteration, as they do not occur normally in the drug (Facchini *et al.,* 2007).

Basic properties of most of the alkaloids are related to each other with a heterocyclic tertiary nitrogen ring, with few exceptions such as paclitaxel, caffeine, *etc*. With reference to the chemical classification of amines, the alkaloids are also named with the suffix -ine (due to the presence of the amino group in an aromatic cyclic ring). In pure form, alkaloids are generally crystalline solid, bitter in taste, colourless, non-volatile, and pungent in smell. Unlike other plant metabolites, the diverse types of its alkaloids have been synthesized independently as a product of its unique biosynthetic pathway. It makes sense to suggest that phytochemicals exhibit higher diversity than synthetic compounds due to the limited chemical space covered by synthetic compounds (Pratap *et al.,* 2021).

However, due to the importance of these metabolites in many biological activities exploited as narcotics, stimulants, and in many pharmaceutical companies for drug discovery. Opium poppy is one such plant that has been studied for its medicinal and narcotic properties. The plant possesses many medicinally important metabolites, especially in the latex of the capsule. The latex has more than 100 alkaloids, among which the Morphine ($C_{17}H_{19}NO_3$) contain 10-20%, methyl morphine or codeine ($C_{18}H_{21}NO_3$) range 2-6%, dimethyl morphine or thebaine ($C_{19}H_{21}NO_3$) found 1-3%, oripavine ($C_{18}H_{19}NO$) range 1-2%, narcotine or noscapine ($C_{22}H_{23}NO_7$) contains 2-10% and papaverine ($C_{20}H_{21}NO_4$) 1-4% are the major ones (Frick *et al.,* 2005; Shukla *et al.,* 2010) (Figure 2). These plants contain primary, secondary, neutral elements and organic acids compounds (Mani and Dhawan, 2011) (Table 1).



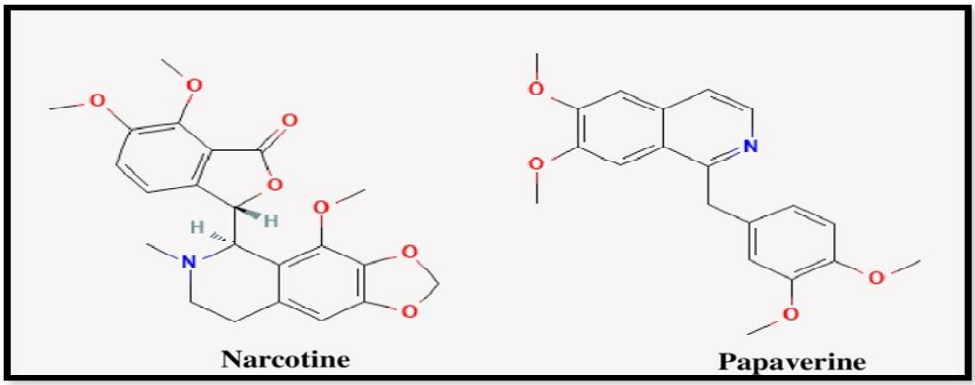


Figure 2: Chemical structure of opium alkaloids.

Table 1: Chemical compounds division in opium poppy

Primary compounds	Secondary compounds	Neutral elements	Organic acid
Morphine, thebaine, codeine, papaverine, narcotine or noscapine, pseudomorphine, narceine, protopine, cryptopine, laudanine, codamine, meconidine, rhoeadine, laudanosine, meconidine, nascopine, lanthopine, hydrocatarnine, xanthaline (Mani and Dhawan, 2011).	Desoxycodeine, thebamine, apomorphine, rhoeadenine, apocodeine, prophyroxine, catarnine (Mani and Dhawan, 2011).	Meconoidin, meconin, opionin (Mani and Dhawan, 2011).	Caffeic acid, ferulic acid, lactic acid, meconic acid (Mani and Dhawan, 2011).

3. Classification of opium poppy alkaloids

Opium poppy alkaloids divided into two major groups found in benzoisoquinoline alkaloids and phenanthrene alkaloids: (a) Benzoisoquinoline nucleus contains (narcoteine or noscapine and papaverine), (b) phenanthrene nucleus contains (thebaine, oripavine, codeine and morphine) and also called as morphinane alkaloids (Raymond, 2004). Pharmacologically, formed as on mode of action (central nervous system, CNS) in animals as stimulants or depressants, sympathomimetics, analgesics, purgatives, *etc.,* that (CNS) (Table 2). This type of classification is independent of the chemical structure of the alkaloids because, the alkaloids having same chemical structure can exhibit different physiological action. For example, Morphine, codeine, and thebaine are highly addictive, analgesic, while papaverine and noscapine (narcotine) work in order to relax and smoothen the muscles (Phillipson and Supavita, 1983; Dey *et al.,* 2020).

Table 2: Major alkaloids of opium poppy and their pharmaceutical role

Opium poppy alkaloids	Pharmaceutical implementation	Details
Morphine	Narcotic analgesic	A prohibited narcotic component of opium (Naqvi *et al.,* 2009; Schrijvers *et al.,* 2010).
Codeine	Antitussive and analgesic	Codeine is controlled substance. Codeine is a morphine prodrug. After taken orally, it is changed into morphine by a liver enzyme, most notably CYP2D6 (Srinivasan *et al.*, 1997; Vree *et al.,* 2000; Chung, 2005).
Thebaine	Precursor of opioids	Thebaine is also a controlled substance. The pharmaceutical industry uses thebaine, a biosynthetic intermediary of morphine, to make oxycodone, oxymorphone, buprenorphine, and naloxone (Aceto *et al.,* 1999; Shukla and Singh, 2004; Yadav *et al.,* 2005).
Narcotein (noscapine)	Antitussive (cough suppressants)	Noscapine is not a controlled substance. This substance might have anticancer properties (Ebrahini *et al.,* 2003; Mahmoudian and Rahimi, 2009).
Papaverine	Antispasmodic	A controlled substance is not papaverine. It is primarily used to treat visceral spasms and vasospasms, particularly those that affect the bowels, heart, or brain. It is also occasionally used to treat erectile dysfunction (Bella and Brock, 2004; Tang *et al.,* 2004; Desvaux, 2005; Brisman *et al.,* 2006).

4. Opium poppy biosynthesis pathway

Alkaloids may also offer a line of defence against animals and insects, according to certain theories. It is may also act as a storage space for compounds that plants frequently use (Wink, 1999). The biosynthesis enzymes were separated from the parietal area in sieves element which are close to laticifers (Larson *et al.,* 1988; Ziegler *et al.,* 2009). Three most enzymes involved in the synthesis of morphin, (S)-N-methylcoclaurine 3-hydroxylase (CYP80B1), berberine bridge enzyme and codeinone reductase (COR). Tyrosine amino acid the

starting product of a large family of alkaloids including isoquinoline (papaveraceae, berberidaceae and ranunculaceae). L-tyrosine undergoes oxidative deamination, followed by decarboxylation, to produce 4-hydroxyphenylacetaldehyde. Additionally, L-tyrosine undergoes decarboxylation to produce tyramine, which is then oxidised to produce dopamine. The biosynthesis begins with the condensation of dopamine and 4-hydroxyphenylacetaldehyde by the enzyme norcoclaurine synthase, which results in (S)-norcoclaurine. However, norcoclaurine 6-O-methyltransferase (6OMT) and coclaurine N-methyltransferase (CNMT) convert (S)-norcoclaurine to (S)-N-methylcoclaurine which converts to(S)-coclaurine on methylation of the former (Dang and Facchini, 2012; Alagoz *et al.,* 2016; Boke *et al.,* 2015). The benzyl isoquinoline alkaloid papaverine, the phthalideisoquinoline alkaloid noscapine, and the morphinans morphine, codeine, and thebaine are all synthesised from (S)-cocularine. (S)-cocularine provides the main precursor for the formation of morphinaian alkaloids is (S)-reticuline, which upon epimerization results in (R)-reticuline molecules. The penultimate stage in the biosynthesis of morphine is the conversion of (-)-codeinone to (-)-codeine by the NADH-dependent enzyme codeinone reductase (COR) (Beaudoin *et al.,* 2014; Shamshina *et al.,* 2018) (Figure 3).

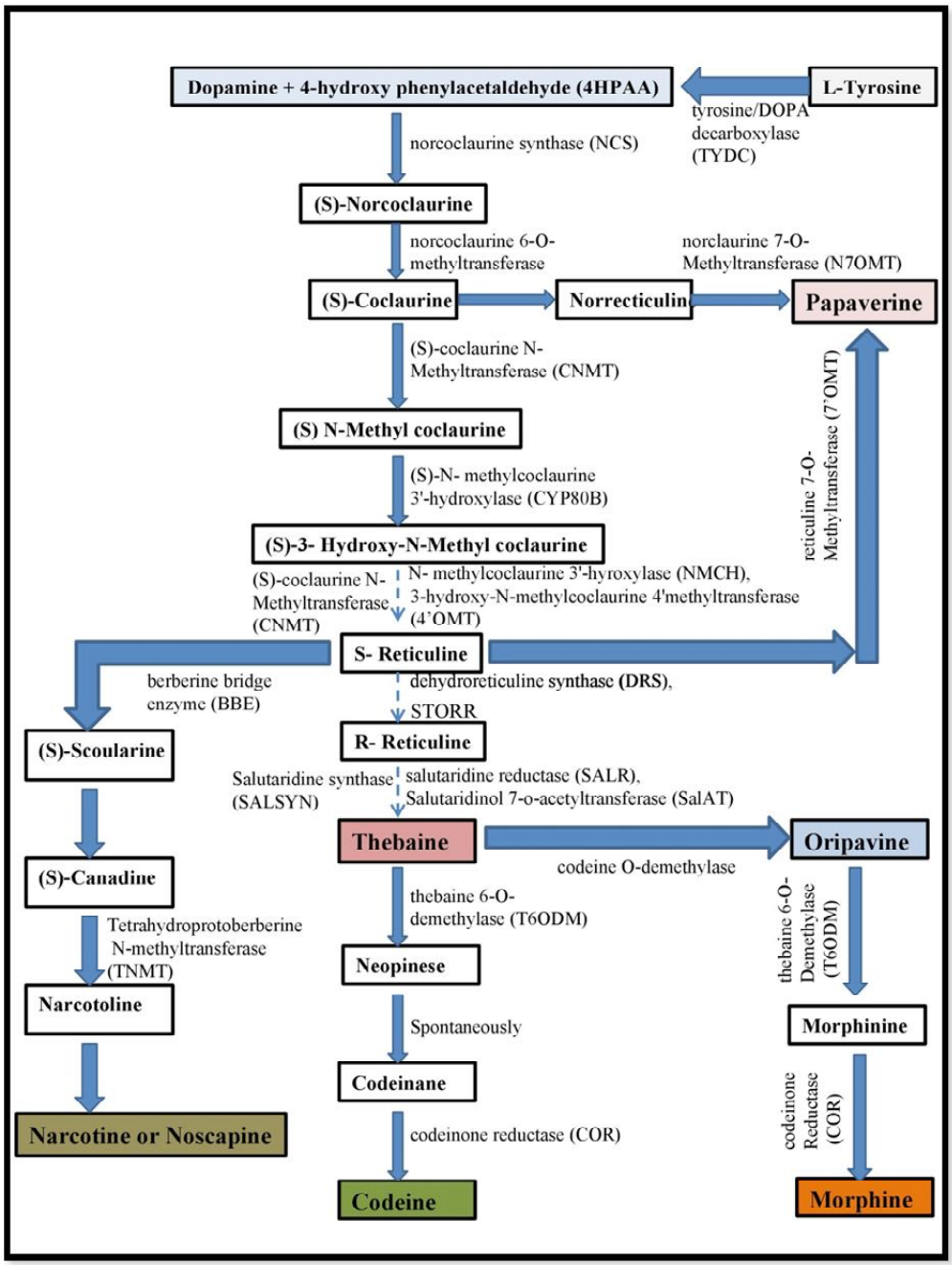


Figure 3: Biosynthesis pathway of major alkaloids in opium poppy.

5. Opiate's therapeutic properties and physiological effects

Since before the dawn of civilization, people have been aware of the pharmaceutical properties and economic significance of various alkaloids, *i.e.,* (BIAs). The opium (latex) formed in laticifers, perforations occur between the side walls of adjacent cells, establishing adjoining links of latex vessels cells present in the epidermis layer of capsules produce abundant amounts of latex when damaged as its cellular contents are under tremendous pressure like sieve elements of the phloem (Nessler and Vonder, 1990; Ziegler *et al.,* 2009). Morphine, thebaine, and codeine are primarily synthesized in internal secretory cells of unripe fruits and accumulate in roots also (Facchini and De Luca, 1995).

Opium has been the primary recognised painkiller for many centuries, and it has been used in many different ways and under many various names (Shukla *et al.,* 2015). For instance, laudanum was an alcoholic solution (diluted solution) of opium that was employed as analgesics and sedative in European medical practice. Because it relaxes the gastrointestinal tract, paregoric, a camphorated opium solution, was the drug of choice for doctors to treat diarrhoea. While morphine was identified in 1804 and heroin was found in 1898 as a result of processing morphine with acetic anhydride, heroin is five to eight times as potent as morphine in terms of its ability to relieve pain and its propensity for addiction. Codeine, a natural alkaloid found in opium that is used to treat coughs, has just one-sixth the potency of morphine. Since the late 1930s, many synthetic medicines with the same analgesic effects as morphine and heroin have been created, collectively known as synthetic opioids. These synthetic drugs include meperidine (demerol), methadone, levorphonal and many others (Shamshina *et al.,* 2018).

Opiates and several naturally occurring endorphin producing chemicals that have an impact on the brain. Because endorphins inhibit specific receptors on specific neurons that convey nerve impulses in order to diminish pain and increase mood, opiates can mimic the effects of endorphins in decreasing the transmission of pain signals within the nervous system. The spinal cord and brain are where opiates like morphine, codeine, and thebaine have their greatest impact. These drugs can also lessen anxiety, increase mood, induce relaxation, tiredness, and sedation, as well as provide a feeling of euphoria or another improved mood. Additionally has a significant physiological effect, such as their ability to relax the smooth muscles of the gastrointestinal system, inhibit the cough reflex, reduce breathing and heart rate (Da Cheng *et al.,* 2015).

Opium is the most lucrative substance due to the widespread usage of two primary drugs, *i.e.,* morphine and codeine, in medications. These two alkaloids, however, have a strong hypnotic and sedative effect. They are mostly given for their astringent, expectorant, diaphoretic, antispasmodic, pain reliever, and calming effects. They are also used for certain types of cough due to their expectorant, diaphoretic, sedative, and antispasmodic qualities. It stimulates central nervous system when taken in a very small dose. Irrespective use in humans, opium and morphine does not show calmative and hypnotic effects in animals, if applies locally it reduces pain and spasm. The Donald Danfold Plant Science Centre's Prof. Tony Kutchan and M.H. Zenk recently demonstrated that the human brain produces trace amounts of morphine through a biochemical pathway that is distinct from that used by poppies. The major opium alkaloids with their effects on human body are described in morphine activity of the involuntary muscles in the biliary, gastrointestinal, and urinary tracts, it can cause constipation, gall bladder spasms, and urinary retention. Codeine is mainly used as an antiperistalsis, analgesic, antitussive, sedative, and narcotic. Thebaine releases histamine and initiates vasodilation. Higher doses result in seizures, while low level reduces intraocular pressure. Narcotine is served as an antitussive, anticonvulsant and narcotic also increases the intraocular pressure. Laudanosine used as a spasmolytic, has a visible contradictory effect on phenobarbital and originates convulsions. Papaverine is employed in the treatment of dilates cerebral vessels, which makes it useful in the treatment of cerebral ischemia; additionally, it raises intraocular pressure, causes mydriasis, and is also used as a spasmolytic (Gennaro *et al.,* 1956). Cryptopine has used as antitussive activity and is a compound that creates dilation of the coronary arteries (Mani and Dhawan, 2011). Additionally, it reduces blood pressure, stimulates respiration, reduce the tonicity of muscles and if consumed in low doses it decreases the intraocular pressure. Protopine decreases the intraocular pressure (Gennaro *et al.,* 1956).

Opium poppy (*P. somniferum*) contains a flavonoid similar to kaempferol, an antispasmodic and diuretic (Borkowski, 1960). Two more flavonoids found in plants, pelargonidin and anthocyanidin, (Ullsperger, 1953). Caffeine, molecule, reduces blood sugar levels (Loof, 1966). Other substance, such as ferulic acid, which slows down the pace at which some brain enzymes react. Thus, flavonoid and all the alkaloids are responsible for the opium sedative and antispasmodic properties. The additive and antagonist physiological actions of the drugs make the anticipated pharmacological effects of opium intake complex.

6. Biochemical analysis

Acetic acid is used as a solvent to extract alkaloids from dried samples (2.5 %) (Ayyangar and Bhide, 1986). When a centrifuge machine is used for 30 minutes at an RPM of 5000, supernatant layer is separated and filtered with a G3 sintered filter. Three times through this process, the extract contains 100 ml of acetic acid (Reddy *et al.,* 2003). Commonly opium alkaloids are quantified through liquid chromatography, mass spectroscopy (LC-MS) (Powers *et al.,* 2018), high performance liquid chromatography (HPLC) (Ahmadi *et al.,* 2013; Krenn *et al.,* 2000), gas chromatography (GC) (Furmanec, 1974), gas-liquid Chromatography (GLC) (Brochmann and Svedsen, 2006), capillary electrophoresis (Bjornsdottir *et al.,* 1995), Paper chromatography (Fairbairn and Wassel, 1963), thin layer chromatography (TLC) and nuclear magnetic resources (NMR) (Carlin *et al.,* 2017). Among this capillary electrophoresis is considered as modern technique and less than GC, HPLC and GLC. Alkaloids are separated and detected using RP (reverse phase) HPLC on porous stationary phases in a smooth manner. A particular content of major alkaloids was found after a 20 min analysis (Shukla *et al.,* 2006). The mobile phase for the HPLC analysis used a 60:40 acetonitrile-water solution containing 0.8 per cent heptafluorobutyric acid and 0.1 per cent aqueous heptafluorobutyric acid. A solution of sodium salt of 1-heptane sulfonic acid (1.0 gm) in water (390 ml) with a pH adjusted to 3.2 using orthophosphoric acid (=solvent A) and acetonitrile (=solvent B) was the other approach for eluting opium alkaloids (Krenn *et al.,* 2000).

It is also possible to separate important opium alkaloids using the capillary electrophoresis technique. Acetonitrile-water 1:1 is

comparable to running spare with ammonium acetate 100 mM at 3.1 pH when examined under UV light at 224 nm. Mass spectroscopy using capillary electrophoresis was also discovered thebaine stronger lipophilic characteristics indicated by methyl group over hydroxyl group (Unger *et al.,* 1997). The best voltage for both is 15 kV when acetonitrile is replaced with CH_3OH and CH_2COONH_4 with CH_3COONa as the run at 3.1 pH for good separation peak. Capillary zone electrophoresis revealed the percentage concentrations in g percentages in five crude samples of gum opium was in the range of 3.85-5.77 (narcotine), 14.45-15.95 (morphine), 0.92-2.37 (papaverine), 2.0-3.5 (codeine), 1.32-2.73 (thebaine) (Reddy *et al.,* 2003).

While different chemical experiments (Garrat *et al.,* 1957) are carried out to gain a thorough understanding of these compounds, which is required for opium quality analysis. The opium identification test is included meconic acid and porphyrine tests, as previously stated. Other tests, such as those for opiates such as morphine and codeine, produce a purple-violet colour, narcotine contain yellow colour, and no colour change with papaverine. The United Nations has utilised Mecke and Frohde tests, which are comparable to Marquis tests and are used for the best qualitative examination for opoids smuggling. Additionally, anions assays are carried out, including checks for the ions chloride, sulphate, citrate, and tartarate (Frick *et al.,* 2005). Meconic acids found in opium poppy are found either in ionized state (meconate) or in unionized state as like the genus *Meconopics* and *Roemaria*. Analysis detects red colour; the colour does not alter even when the test solution contains 10% ferric chloride. The trace alkaloid porphyrixine, which turns dark red colour used to analyse the chemical composition of opium.

7. Important role of poppy

Traditionally, opium poppy has been widely used as the traditional medicine or drug throughout India due to the presence of many medicinal compounds. The plant is utilised for its analgesic alkaloids. The poppy plant is a flowering plant that is frequently used as garden ornamentation due to its lovely flowers, which are frequently pink, red, white, purple, or orange. Poppy seeds are used as a nutraceutical, spice and in baked goods. The seeds are also used in cakes and on top of bagels commercially. This plant seed oil used as a carrier for many parenteral formulations as well as a salad, cooking, and oil for drying artwork (Mishra *et al.,* 2013). Poppy leaves are used as a vegetable.

Opium, a highly addictive narcotic drug. The unripe pod is traditionally sliced open so that the sap (latex) can pour out and dry on the outside of the fruit. Morphine, codeine, thebaine, narcotine, and papaverine can be found in the yellow-brown latex scraped from the pod. The central nervous system (CNS) of heroin has euphoric (rush), anxiolytic, and analgesic effects. It is a very addictive substance (Evans *et al.,* 2017).

Morphine compound is responsible for the majority of its analgesic and narcotic effects. Freidrich Wilhelm Adam Serturner extract morphine from the opium plant and gave it the Greek name "Morpheus," which translates to "Morpheus" in English, in recognition of its capacity to alleviate pain (Katzung, 2009). Opium's hypnotic qualities and chemical make-up result in a lower analgesic effectiveness than pure morphine. Since most opioids also have euphoric, sedative, or respiratory depressant properties, there is a high level of tolerance to all of these side effects. The way morphine displays its efficacy is by imitating naturally occurring endogenous opioid peptides, given that it is a complete agonist, endorphins, and enkephalins at a μ receptor in CNS. These opiates or alkaloids four kinds of enzymes mediate its pharmacological action receptors belonging to the class of G-proteins known as μ, δ, σ and κ (Champe *et al.,* 2005) and pair of receptors (Waldhoer *et.al.,* 2004). In comparison to morphine, codeine is a milder analgesic and cough suppressant. Papaverine is beneficial in treating hypertension because it causes a noticeable vasodilation. It is also used to treat angina pectoris and abort uremic crises (De Takats, 1936). Noscapine, another isoquinoline alkaloid, has antitussive properties (Segal *et al.,* 1957), as well as being antineoplastic or anti-mitotic (Mahmoudian and Rahimi, 2009); it slows the growth of tumour cells by targeting tubulin, which results in aberrant mitotic spindle assembly (Joshi and Zhou, 2000).

8. Conclusion

Opium poppies have numerous medical applications, and they also have great value as a food-grade crop along with its potential medicinal uses. Alkaloids, phenolic compounds, and essential oils are just a few of the pharma coactive extracts. These substances are in charge of the diverse biological functions including its analgesic, anticancer, antioxidant, and antibacterial properties. To learn more about the active compounds in these plant extracts or to determine whether there is a synergism that makes use of the complete extracts more attractive, pharmacological investigations of these extracts should be supported by characterisation studies. Biochemical analysis used to determine the overall profile of the poppy plant extracts and other parts have an impact on the phytochemical composition, content, and bioactivity analysis also. The extraction technique, the extraction's input variables, and the way the sample is prepared for analysis are all aspects that affect the phytochemical profile. Overall, further research should focus on fractionation and pharmacological tests in addition to a better understanding of active compounds thorough characterization.

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Conflicts of interest

The author declares no conflict of interest relevant to this article.

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