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Papaver somniferum: Phytochemistry, biological activity and toxicology; a review

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Abstract
Opium poppy (*Papaver somniferum*), a flowering plant with the annual herbaceous habit belonging to the *Papaveraceae* family, is native to Eastern Mediterranean. The plant has a very long tradition of use as a medicinal herb since the early Neolithic. The commercial importance of the plant derives primarily from its medical properties. The plant's phytochemistry revealed secondary alkaloid metabolites such as morphine, thebaine, codeine, noscapine, papaverine and sanguinarine. Besides these, flavonoids, triterpenoids, steroids, phenylpropanoids, free amino acids and sugars are also found. The pharmaceutical companies widely utilize these phytochemical constituents for producing medicine with analgesic, antitussive, sedative, antispasmodic and antitumor effects. Diverse pharmacological activities have revealed that this plant is a model in discovering significant biosynthesis steps of valuable pharmaceutical compounds. This review will provide an exploration of the phytochemistry, biological activities and toxicology of *Papaver somniferum.*

Keywords: alkaloids, codeine, morphine, papaverine, noscapine, thebaine

Introduction

Papaver somniferum (2n = 22) of the family *Papaveraceae* and genus *Papaver* is a flowering plant with an annual herbaceous habit of erect glaucous rarely branched greyish-green stem, growing to a height of 60 – 120cm (Masihuddin *et al*. 2018) [24].

Leaves are thin, glabrous, serrate and broadly lanceolate with acute apex, semi-amplexicaul cordate leaf base and arise alternately. The plant is monoecious and reproduces only sexually.

The inflorescence is solitary and terminal. The flowers are complete, bisexual and vary in colour from pure white to reddish-purple. Pollination is entomophilous. Fruit is a globular ovoid capsule. Seeds are reniform, white or greyish-black (Masihuddin *et al*. 2018) [24]. The diarch taproot system with numerous lateral branches is present.

Papaver somniferum is an outstanding medicinal plant known for its therapeutically beneficial secondary metabolites, particularly a diverse group of benzylisoquinoline alkaloids (Labanca *et al*. 2018) [23]. The medicinal value of *Papaver somniferum* is due to the presence of more than 30 alkaloids (Acharya *et al*. 2009) [1]. The plant is the lone commercial source of narcotic analgesics, codeine and morphine. Apart from these, the plant also produces other benzylisoquinoline alkaloids with potent pharmacological properties, including vasodilator papaverine, antimicrobial agent sanguinarine, cough suppressant and potential anticancer drug noscapine. The edible seeds of the plant are used in the culinary field, in bakery products and for oil (Vasek *et al*. 2020) [39]. However, its dark side is infamously the abuse of its sap (opium) for heroin production.

Phytochemistry

Papaver somniferum is valued for its alkaloid content. The plant is a source of many pharmaceutical benzylisoquinoline alkaloids, including morphine, codeine, noscapine, thebaine, papaverine and sanguinarine (Hosseini *et al*. 2011) [19]. The other constituents found in the plant are steroids, triterpenoids, flavonoids, phenylpropanoids, free amino acids, essential oil (Cheng *et al*. 2015) [5]. The sugars detected are fructose, glucose, xylose, maltose, and arabinose, and the concentration of reducing sugars (14.50%) is higher than that of non-reducing sugars (3.62%). Qualitative examination revealed the existence of a basic amino acid (arginine), aromatic amino acids (*viz*, tyrosine, tryptophan phenylalanine), and a sulphur-containing amino acid (cysteine). Lipid fractions reported from the plant were sterol ester, monoglyceride, 1, 2-diglyceride, 1, 3-diglyceride, triglyceride and sterol. Vitamin A (retinol) and C (ascorbic acid) were also reported. Opium is also rich in several acids like meconic acid (10%), citric acid, lactic acid, malic acid, tartaric acid, acetic acid, succinic acid, phosphoric acid and sulphuric acid (Masihuddin *et al*. 2018) [24]. Enzymes such as protease, peroxidase, lipase and phospholipase were also found (Bozan and Temelli 2008). The poppy seed oil is rich in protein and contains saturated palmitic, stearic, myristic and lauric acids and unsaturated fatty acids such as oleic, linoleic, alpha-linolenic acid (Untoro *et al*. 2006) [36]. The ash of opium contains several minerals like potassium (28.04%), calcium, phosphorous, sodium, magnesium, sulphur, iron and aluminium.

Phytochemical Constituents

Table 1

Secondary Metabolites	Phytoconstituents
Alkaloids	Morphine, Codeine, Thebaine, Noscapine, Papaverine, Sanguinarine (Hosseini *et al*. 2011) [19].
Sugars	Glucose, fructose, maltose, xylose and arabinose.

Lipids	Monoglyceride, 1, 2-diglyceride, 1, 3-diglyceride, triglyceride and sterol.
Free amino acids	Tyrosine, tryptophan, phenylalanine, cysteine, arginine.
Enzymes	Protease, peroxidase, lipase and phospholipase (Bozan and Temelli 2008).
Fatty acids	Oleic acid, linoleic acid, linolenic acid, palmitic acid, lauric acid, myristic acid and stearic acid (Untoro *et al*. 2006) [36].
Organic acids	Meconic acid (upto10%), lactic acid, citric acid, malic acid, tartaric acid, acetic acid, succinic acid, sulphuric acid and phosphoric acid (Masihuddin *et al*. 2018) [24].
Vitamins	Vitamin A (retinol) and C (ascorbic acid).
Minerals	Potassium (28.04%), calcium, phosphorous, sodium, magnesium, sulphur, iron, aluminium.

Biological Activity

Papaver somniferum is medicinally an essential source for many pharmacologically active alkaloids (Cheng *et al*. 2015) [5]. The plant has been investigated for various biological activities. The dried latex, called opium, obtained from the capsule of the plant, has traditionally been used as a natural base for opioid drugs. The opium contains analgesic (thebaine, codeine, morphine) and therapeutic alkaloids like sanguinarine and papaverine (Mani and Dhawan 2014) [25].

Analgesic Activity

Opium provides basic chemical structure for all opiates and has long been used for pain relief since times. Opium is a central nervous system depressant and narcotic analgesic (Cheng *et al*. 2015) [5]. Opium's analgesic effect is most important medicinally and the class is mainly used for its analgesic properties and, more specifically, in chronic pain conditions like cancer. Despite the progresses in pain therapies, an effective, safe forceful and effective analgesic drugs is the requirement for treating different painful conditions, primarily chronic pain (Pires *et al*. 2009) [27]. Opium acts on specific receptors of the CNS. The action is to integrate painful messages sent by sensitive nerves, thereby blockage of the painful signal.

Hypnotic Activity

The oldest known hypnotic agent used by humans is opium. It is unexcelled as a hypnotic and sedative and frequently administered to reduce anxiety, induce calm (sedative effect), and induce sleep (hypnotic effect). Opium has been used as a tranquillizer for centuries (Eric *et al*. 2006) [13]. Hypochondriasis and hysteria were treated by it in early times and since then it has found its use in mania and melancholia treatment. Avicenna also mentioned its use for insomnia treatment and suggested small dose use of opium in combination with supplementary agents for this purpose.

Antitussive Activity

Narcotic antitussives such as codeine are one of the most widely and frequently used antitussive to cure symptoms of flu, common cold, hay fever, allergies, and other breathing illnesses like sinusitis and bronchitis (Schmidt *et al*. 2002) [33]. Codeine's antitussive effect is primarily revealed through μ-opioid receptor in the CNS (central nervous system) and partly through κ-opioid receptor. These receptors work by inhibiting a coordinating region for coughing located in the brain stem disrupting the cough reflex arc. In combination with other medicines, narcotic antitussives are the most potent antitussives used to treat severe cough. For immediate effective symptomatic respite from dry cough within clinical practices, codeine has proved as the mainstay (Vora and Nadkar 2015) [40].

Anticancer Activity

Current studies have revealed that alkaloids obtained from *Papaver somniferum* can also be used in cancer treatment (Chen *et al*. 2015) [4] and such studies have highlighted the antitumor activity of noscapine through arresting of metaphase and apoptosis induction in dividing cells. Opium alkaloids that show promising results in cancer treatment include noscapine, which has recently been introduced as an anti-mitotic agent and interacts with α-tubulin and has anticancer anti-angiogenetic properties; codeinone, an oxidative product of codeine which has apoptotic effects through fragmentation of DNA; morphine shows anticancer activities by inhibiting Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB). Glioblastoma (GBM), the most destructive kind of prime malignant brain tumour, is induced by HMGB1 (high mobility group box 1) and RAGE (receptor for advanced glycation end-products) interaction and this interaction has been found to inhibited by another anticancer agent, papaverine (Inada *et al*. 2019) [20].

Antimicrobial Activity

The alkaloid extracts of *Papaver somniferum* were effective against fungal and bacterial pathogens. The extracts revealed additional inhibitory properties against fungal than bacterial pathogen and more against gram-positive than gram-negative bacteria (Ismaili *et al*. 2017) [21]. The essential oil of the poppy flower was determined to have antimicrobial effects on all fungal species tested. Hydroalcoholic, aqueous, and ethanolic extracts of poppy seeds were active against 2 acne-causing bacteria, *Propionibacterium acnes* and *Staphylococcus epidermis* (Chaudhary *et al*. 2013) [3]. The antimicrobial agent sanguinarine, quaternary benzo- phenanthridine alkaloid, exhibits strong bactericidal property, particularly on gram-positive bacteria such as *Staphylococci* and *Bacillus anthracis*. The mechanism of action is through sanguinarine's interaction with DNA.

Antiviral Activity

The antiviral effects of *Papaver* alkaloids when tested against several viruses belonging to various taxonomic groups in-vitro, it showed a great impact on their replication (Istatkova *et al*. 2012) [22]. Antiviral effects have been found against human rhinovirus 14 and poliovirus 1 replication through particular alkaloids. Papaverine effectively inhibits several influenza virus strains such as paramyxoviruses parainfluenza virus 5 (PIV5), human parainfluenza virus 3 (HPIV3) and respiratory syncytial virus (RSV) infections. Papaverine significantly effects the morphology of influenza virus. Papaverine also showed potent activity against cytomegalovirus, respiratory syncytial virus, measles and human immunodeficiency virus (Gaber *et al*. 2020) [15].

Muscle Relaxant and Vasodilator Activity

Opium alkaloid, Papaverine, largely is used for coronary and cerebral vasodilation and find its place as an important antispasmodic drug (Fusi *et al*. 2016) [14]. Papaverine is a direct smooth muscle relaxant independent of muscle innervation, mainly if the muscle has been contracted due to vasospasm. It affects the heart muscle and vascular smooth muscles by blocking the non-selective phosphodiesterase and calcium channels. The smooth musculature of the larger blood vessels is relaxed, including the coronary, systemic peripheral and pulmonary arteries (Tang *et al*. 2004) [35]. The resulting vasodilation has been potentially attributed to inhibition of cyclic nucleotide phosphodiesterases, resulting in increased intracellular levels of cyclic AMP and cyclic GMP accompanied by a decrease in Ca^{++}. It is used to treat myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease, cerebral angioplasty states. The alkaloid also acts on the myocardium to depress conduction and irritability and prolong the myocardial refractory period (Ebrahini *et al*. 2003) [12]. The compound is used therapeutically as its hydrochloride salt to relieve cerebral and peripheral ischemia associated with arterial spasm and symptomatic relief of myocardial ischemia complicated by arrhythmias.

Antidiarrheal Activity

Though not known the exact time of opium usage against diarrhoea, Ibn Sina, a Persian physician described its use around 1000 A.D and has been found to be widely used in China for it (Duarte 2005) [11]. Opiate antidiarrheal drugs are widely used therapies for the treatment of diarrhoea. Use of such drugs under close monitoring have proved to be safe and effective in controlling various diarrheal conditions through reducing motility and providing enough absorption time (Schiller 2017) [32]. Opiod agonists both δ and μ, inhibit mucosa's secretion, release acetylcholine within myenteric plexus**,** and through reduction of neuronal excitability blocks distention-induced peristaltic contractions. Muscle tone is altered, and non-propulsive motility patterns become more common (Galligan and Akbarali 2014) [16].

Edible Uses

Poppy seeds are also appreciated in the culinary field, in bakery products and for oil. Seeds (raw or cooked) are used as a flavouring in cakes, bread, fruit salads. The crushed and sweetened seeds are used as a filling in crepes, strudels, pastries (Labanca *et al*. 2018) [23]. Highly nutritious seeds contain about 22.7% protein, 48% fat, and 9.8% carbohydrate, and are good source of lecithin. Poppy seeds contain many plants derived chemical compounds that are found to have antioxidant, disease-preventing and health-promoting properties. The seeds are especially rich in linoleic and oleic acids. They are an excellent source of B-complex vitamins such as thiamine, pantothenic acid, pyridoxine, riboflavin, niacin and folic acid (Raut and Ghotankar 2019) [29]. In some countries, young leaves are eaten either raw or cooked at the seedling stage.

Toxicology

Papaver somniferum acts as a significant renewable reserve for various physiologically active pharmaceutical alkaloids (Verma *et al*. 2019) [38]. Opioids action on the opioid receptors (μ, κ, δ), have several advantageous therapeutic effects but also may cause numerous harmful effects, including opioid dependence, respiratory depression, sexual dysfunction, cognitive and neuromuscular disturbances, nausea and vomiting, sedation, constipation, urinary retaining (Dahan *et al*. 2010) [7].

Opioid Dependence

Opioids are powerful painkillers that are highly addictive. Opioids are prescribed to treat pain. With prolonged use, pain-relieving effects may lessen, and the body can develop dependence. Opioid dependence affects nearly 5 million inhibitants of US and leads to approximately 17,000 deaths annually (Dixon 2020) [10]. Opioid addiction or dependence, a chronic, recurrent disease changes neurotransmitter systems in the CNS. Mesocorticolimbic dopaminergic system activation occurs by opium alkaloids projecting upto medial prefrontal cortex and nucleus accumbens from ventral tegmental area, leading to dopaminergic system activation causing sustained opiod dependence and consumption (Demirkapu and Yananli 2020) [9].

Respiratory Depression

Administration of exogenous opioid analgesics increase the vulnerability of ventilatory control system and a possible fatal complication, respiratory depression can arise by opoid over-doses or consumption along with other depressants (Dahan *et al*. 2018) [7]. μ-opioid receptors, present on neuron surfaces within brainstem respiratory centers are activated by opioids and lead to respiratory depression (Dahan *et al*. 2010) [7]. Activation of these opioid receptors by exogenous opioids may initiate respiratory compromise, which is usually short-lived and reverts to regular breathing activity. In some cases, often due to an opioid overdose or the combination of opioid with other centrally depressant drugs, it diminishes breathing progress into irregular breathing and eventually into apnea (the complete cessation of breathing) leading to cardiorespiratory collapse and ultimately death (Schrier *et al*. 2017) [37].

Cognitive and Neuromuscular Disturbances

Opioid abuse can lead to acute or chronic cognitive disturbance. Successful opioid therapy often depends on achieving a balance between analgesic effectiveness and side effects. Non-human animal research points to opioid modulation of cognitive and decision-making processes (Steenbergen *et al*. 2019) [34]. Common short-term effects include memory loss, a state of confusion, and a lack of coordination. Long-term effects include increasing loss of declarative memory, a general lack of emotional stability and control over one's action. Different mechanisms are proposed for neuromuscular disturbances caused by opiate consumption. Accumulation of neuroexcitatory opioid metabolites may have a relevant role in producing this unwanted effect. In general, opium causes memory loss and reasoning dysfunction (Heydari *et al*. 2013) [18].

Sexual Dysfunction

Sexual dysfunction is a prevalent disorder in opioid-dependent males (Saberi Zafarghandi *et al*. 2016) [30]. Opioids may decrease sexual function because they affect hormones in the hypothalamic-pituitary-gonadal pathways. These control the production of sex hormones by secreting GnRH (Gonadotropin-releasing Hormone). Inhibition of GnRH by Opioids, leads to a decrease in the production of luteinizing hormone and inhibiting testosterone production

(Railton 2019) [28]. The decline in testosterone levels leads to sexual and erectile dysfunction, one of the most relevant side effects of opioid analgesics. This effect is mediated through the direct agonist action on the μ-receptors (Mattoo *et al*. 2020) [26]. This effect is considered part of the broad opiate-induced neuroendocrine dysfunction that causes an imbalance in the levels of sexual hormones.

Nausea and Vomiting

Opioids are the mainstay of cancer pain treatment as supported by the WHO's (World Health Organization) analgesic hierarchy for cancer pain relief (Sande *et al*. 2019) [31]. Opioid treatment is a standard and consolidated therapy for relieving pain in advanced cancer patients. Patients using opioids for acute pain struggle with opioid-induced nausea and vomiting (Colombo *et al*. 2020), well-acknowledged opioid-induced effects possessing central and peripheral components. μ- receptors within CTZ (Chemoreceptor Trigger Zone) of the medulla oblongata are activated leading to stimulating vomiting under low opiod doses. Vomiting and nausea induced by opioids is supposed to occur through CTZ and vestibular stimulation and digestive tract motor stagnation. These side effects lead to fatigue, anxiety, and worse quality of life and directly impact patient outcomes (Giusti *et al*. 2019) [17].

Conclusion

Papaver somniferum is a plant of temperate climate but can be grown during winter in subtropical regions. The plant produces mainly two products: opium and seeds. Nearly every plant part contains milky white latex (opium), the unripe capsule contains a large amount. Among the various drugs of medicinal importance, opioids are an important class of compounds produced by the plant. It *is* the primary source of diverse physiologically active alkaloids. Though synthetic production of several medicinal compounds can be done, alkaloids like Phenanthridine (morphine, codeine, the baine), Benzylisoquinoline (papaverine) and Phthalideisoquinoline (noscapine) are only obtained from opium which places *Papaver somniferum* at the highest place among the diverse array of medicinal plants. The main alkaloids include narcotic and analgesic morphine and codeine, the mild analgesic and sedative thebaine, the antitussive and apoptosis inducer noscapine, the vasodilator papaverine and the antimicrobial agent sanguinarine. These opioids interact with opioid receptors present in the CNS and peripheral tissues to bring about medicinal effects. Opium alkaloids are potent pharmaceutical drugs, but their use is limited because of dependence and withdrawal. Extensive studies on *Papaver somniferum* are required to enlist all the possible benefits obtained from the plant. There is scope for developing new therapeutic drugs from *Papaver somniferum* and the research that will pave the way for its commercial utilization.

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