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Therapeutic Applications and Risks of Papaver *Somniferum L.* Alkaloids in Cancer Pain and Acute Cardiogenic Pulmonary Oedema

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ABSTRACT

Background: Papaver somniferum L. (opium poppy) is a historically significant medicinal plant, primarily known for its potent alkaloids such as morphine, codeine, and thebaine. With the global rise in opioid use and misuse, understanding the medical potential and risks of poppy-derived compounds has gained renewed significance, particularly in contexts such as cancer-related pain and acute cardiogenic pulmonary edema (ACPE).

Purpose: This review evaluates the efficacy and pharmacological mechanisms of P. somniferum alkaloids, particularly morphine, in managing cancer-related pain and acute cardiogenic pulmonary edema (ACPE), alongside associated risks and regulatory concerns.

Method: A literature review was conducted, synthesizing data from peer-reviewed studies sourced from PubMed, Google Scholar, Scopus, and Web of Science, focusing on pharmacological, clinical, and biochemical properties of poppy alkaloids.

Results: Morphine effectively controls severe cancer pain (80–90% pain reduction in clinical trials) via mu-opioid receptor modulation but is underutilized due to addiction concerns. In ACPE, morphine reduces preload and anxiety but lacks clear survival benefits, with risks like respiratory depression (10–15% incidence) and drug interactions.

Conclusion: While Papaver somniferum-derived morphine remains a cornerstone in palliative pain management, its use in ACPE should be approached cautiously due to unclear survival benefits and notable risks.

1. Introduction

Many plants naturally contain beneficial phytochemicals that can significantly help in treating various diseases and health issues, and they can also serve as alternatives to synthetic drugs. This also applies to the Papaver genus (family Papaveraceae), which has been recognized for its therapeutic capabilities due to its phytochemical composition. (Butnariu *et al.*, 2022)

The term "poppy" has been used for the Papaveraceae family, but it is simply part of the complete name of the opium or oil poppy. The opium poppy belongs to the Papaver section, Papavereae tribe, and Papaveroideae subfamily. A key characteristic of this plant family, excluding its seeds, is the presence of a watery and milky latex found within its vessels. (Hayat *et al.*, 2023)

The opium poppy, a cultivated form of *Papaver somniferum*, is a crucial source of opium (the dried liquid extracted from the poppy's fresh fruit after it's cut) and poppy seeds. Because morphine, the main alkaloid in opium poppies, has narcotic qualities, the United Nations and the national governments where they are grown regulate their cultivation. However, in Afghanistan, Pakistan, Burma, Mexico, Laos, and Colombia, illegal cultivation of the opium poppy for opium extraction is widespread. This illegally grown opium is used to extract morphine, which is then turned into heroin in improvised manufacturing facilities. (Baser & Arslan, 2014)

Since ancient times, *Papaver somniferum L.*, sometimes known as the opium poppy, has been utilized medicinally because of the concentration of its secondary metabolites. Benzylisoquinoline alkaloids (BIAs), its most important secondary metabolites, are nevertheless crucial to the pharmaceutical sector. Some of these have specialized medicinal applications and also affect the central nervous

system (CNS) like morphine. (Labanca *et al.*, 2018) There are over 100 species in the *Papaver somniferum L.* genus. Out of these, roughly 80 have been analyzed for their alkaloid composition, leading to the identification of around 140 alkaloids. These alkaloids are isoquinoline-based and produced through biological processes. *Papaver somniferum L.* has the highest concentration of morphine, generally making up 45-90% of its alkaloid content, while other alkaloids are present in smaller amounts. (Sotto *et al.*, 2023)

The opium poppy, *Papaver somniferum*, is a traditional herb in the poppy family (Papaveraceae) that has long been used in medicine. Its key feature is the production of numerous widely used pharmaceutical alkaloids like morphine, codeine, thebaine, and porphyroxine, along with over eighty other alkaloids derived from tetrahydrobenzylisoquinoline. (Masihuddin *et al.*, 2018)

The opium poppy is among the earliest species of plant to be grown for human use. Poppy cultivation and use have been documented for thousands of years, according to archeological findings. But until recently, its origin and history of domestication were unknown. It is challenging to discern between domesticated and wild forms due to the lack of clarity in domestication traits, particularly in archaeological records. Numerous lines of evidence point to the Mediterranean as the origin and domestication center of poppies, primarily based on data from archeological digs and the geographic distribution of both cultivated and wild species. (Jesus *et al.*, 2021; Salavert *et al.*, 2020)

It is thought that characteristics associated with poppy domestication include variations in seed and capsule sizes as well as capsule indehiscence. (Zohary *et al.*, 2012) Nowadays, poppies are grown extensively throughout South America, Asia, Oceania, and Europe as both legal and illegal crops. (Beaudoin & Facchini, 2014; Hong *et al.*, 2022; Tamiru-Oli *et al.*, 2018)

This plant serves as a source of various benzylisoquinoline alkaloids that are utilized in the illegal production of heroin and the pharmaceutical industry. These alkaloids include papaverine, morphine, thebaine, noscapine, and codeine. Additionally, the plant's seeds—known as poppy seeds—are utilized in the culinary sector for edible oil extraction and baking. Additionally, some countries cultivate poppies as ornamental plants because of their flowers. (Labanca *et al.*, 2018b)

There have been reports of significant genetic diversity in poppies in a number of nations, including Australia, Turkey, India, and the Czech Republic. (Celik *et al.*, 2016; Lahiri *et al.*, 2018; Saunders *et al.*, 2001; Srivastava *et al.*, 2020; Svoboda *et al.*, 2020) In some of these nations, there are collections of germplasm of various sizes. Furthermore, a sizable portion of the genetic resources for poppies are currently kept in international genebanks as seeds. Over 1100 poppy accessions collected worldwide are included in the genebank of the Crop Plant Research (IPK) and Leibniz Institute of Plant Genetics, Germany. A collection of comparable size is maintained at the Slovak University of Agriculture's Institute of Protection of Biodiversity and Biological Safety. (György *et al.*, 2022)

This review explores the therapeutic potential of the plant *Papaver somniferum* and its alkaloids, focusing on their applications in treating cancer-related pain and acute cardiogenic pulmonary edema. It examines the use of morphine, a key alkaloid derived from *Papaver somniferum*, in managing these conditions, while also addressing the associated challenges.

2. Taxonomical Classification

Taxonomical classification of *Papaver somniferum L.* (opium poppy). (Labanca *et al.*, 2018a)

- **Kingdom:** Plantae
- **Subkingdom:** Viridiplantae
- **Infrakingdom:** Streptophyta
- **Superdivision:** Embryophyta
- **Division:** Tracheophyta
- **Subdivision:** Spermatophytina
- **Class:** Magnoliopsida
- **Superorder:** Ranunculanae
- **Order:** Ranunculales
- **Family:** Papaveraceae
- **Genus:** Papaver L.
- **Species:** *Papaver somniferum L.*

3. Chemical Constituents

The Papaver genus is highly valued in the pharmaceutical, food, and ornamental plant industries. Traditional medicine also recognizes the value of these herbs. The most important source of therapeutic phytochemicals among all Papaver species is the opium poppy (*Papaver somniferum L.*), especially alkaloids such as (Butnariu *et al.*, 2022):

- **Morphine:** (7.65%-25.15%)
- **Codeine:** (1.21%-6.37%)
- **Thebaine:** (0.97%-6.38%)
- **Papaverine:** (0.51%-5.33%)
- **Noscapine:** (4.03%-15.22%)

Additionally, Papaver plants contain various phytochemicals that contribute to their biological effects. These include alkaloids, essential oils, and phenolic compounds. (Butnariu *et al.*, 2022)

It also comprises:

- **9-Octadecynoic acid:** (30.72%)
- **9-Tetradecen-1-ol, acetate (E):** (24.02%)
- **9,12-Octadecadienoic acid, methyl ester, (E,E**): (7.82%)
- **cis-9,10-Epoxyoctadecan-1-ol:** (7.43%)
- **Undec-10-ynoic acid:** (4.36%)

Table 1: Key Alkaloids of *Papaver somniferum L.* and Their Properties

Alkaloid	Content (%)	Pharmacological Effects	Clinical Applications	Key Side Effects
Morphine	7.65–25.15	Analgesia, sedation, respiratory depression	Cancer pain, acute pulmonary edema	Addiction, pruritus, respiratory depression
Codeine	1.21–6.37	Analgesia (less potent), antitussive, antidiarrheal	Mild pain, cough, diarrhea	Drowsiness, respiratory depression
Thebaine	0.97–6.38	Convulsant, opioid precursor	Precursor for opioid synthesis	Convulsions, addiction potential
Papaverine	0.51–5.33	Vasodilation, smooth muscle relaxation	Vasospasm, ischemia treatment	Hypotension, cardiac effects
Noscapine	4.03–15.22	Antitussive, mild analgesia	Cough suppression	Hypotension, bronchoconstriction

4. Applications for Chemical Components

4.1. Morphine

Morphine is a primary opium alkaloid that's extracted from the *Papaver somniferum L.* plant. The body processes it into codeine and heroin. This substance produces effects like pain relief, anxiety reduction, a feeling of intense happiness, drowsiness, slowed breathing, and contraction of smooth muscles in the digestive system. It functions by binding to mu (μ), delta (δ), and kappa (κ) receptors, which are located throughout the central nervous system. Morphine is used in anesthesia, to treat sudden fluid buildup in the lungs, and to manage severe pain. (Herman *et al*., 2024)

It can be injected subcutaneously, epidurally, intrathecally, intramuscularly, rectally, orally, and subcutaneously. The rate of morphine absorption varies, with the majority of it occurring in the upper intestine and the rectal mucosa, where it is virtually completely absorbed. Morphine exhibits a notable 17–33% oral bioavailability and first-pass metabolism. The spleen, lungs, skeletal muscle, liver, brain, kidneys, and digestive tract are among the organs that get morphine (Guthrie & Teter, 2016). Morphine-3-glucuronide (M3G, 45–55%) and morphine-6-glucuronide (M6G, 10–15%). Morphine-3,6-diglucuronide, morphine-3-ethereal sulphate, normorphine, normorphine-6-glucuronide, normorphine-3-glucuronide, and codeine are some compounds that are created during the breakdownof morphine by the liver by combining it with glucuronic acid. Both normorphine and M6G actively relieve pain by attaching to opioid receptors. However, M6G, which is produced in larger quantities than normorphine, can increase the pain-relieving effect of morphine. M3G, on the other hand, doesn't enhance morphine's pain-relieving effects because it doesn't bind well to opioid receptors. (Olsen & Sharfstein, 2019)

4.2. Codeine

Opioid receptor stimulation is how codeine and its metabolite, morphine, work. The primary effects include central antitussive, antidiarrheal, and analgesia (less intense than morphine) (Troy, 2005). Additionally, it can cause respiratory depression, drowsiness, and sedation. Codeine is a medication used to treat cough, mild to moderate pain, persistent diarrhea, and restless legs syndrome. Codeine is administered intramuscularly and orally. Oral use results in rapid absorption and increased bioavailability because of a reduced first-pass metabolism (53%). The liver, spleen, and kidneys receive most of the codeine, even though it is distributed throughout the body. (Shimoji & Fujioka, 2020)

In adults, doses of 7–14 mg/kg, and in children, doses exceeding 5 mg/kg, can cause death. A concentration of codeine in the blood of 20–50 μg/dL is considered toxic, and levels above 60 μg/dL are fatal. (Gossel, 2018)

4.3. Thebaine

Thebaine, sometimes referred to as paramorphine, is a chemical used to make other opioids and is not used medicinally. Similar to morphine use, thebaine exposure can cause convulsions similar to those caused by strychnine and become addictive. (Demirkapu & Yananli, 2020)

4.4. Papaverine

Papaverine affects the smooth muscles of blood arteries as well as the cardiac muscle via inhibiting calcium channels

and non-selective phosphodiesterase (Ueda *et al.*, 2023). Papaverine causes the heart's refractory period to lengthen and suppress conduction. Vasodilatation directly affects the coronary and pulmonary arteries' smooth muscle cells. Since papaverine-mediated relaxation in smooth muscles does not rely on muscle innervation, it does not result in muscular paralysis. These effects are more prominent when papaverine is involved, particularly in ischemia with arteriospasm. (Demirkapu & Yananli, 2020)

Papaverine can be administered intravenously, intramuscularly, or orally. In oral use, absorption is almost complete. Because there is approximately 54% less first-pass metabolism, oral bioavailability is higher. Papaverine is distributed throughout the body, but the liver and adipose tissue receive it first. When the liver breaks down papaverine, it produces 6-desmethylpapaverine (6-DMP), which is the main product, and also 4′,6-didesmethylpapaverine (4,6-DDMP) (Wolf *et al.*, 2019). There's no available information on what blood concentrations of papaverine are considered toxic. In rats, the average lethal oral dose is 360 mg/kg, but the corresponding dose for humans is unknown. (Demirkapu & Yananli, 2020)

4.5. Noscapine

Noscapine has a slight analgesic effect and has no effect on morphine withdrawal or morphine-like effects (Chain *et al.*, 2018). Due to the fact that it shares codeine's core antitussive action, it is used to reduce the frequency and intensity of coughs in patients with pulmonary emphysema and bronchial asthma. Noscapine elevated histamine release in the animal study, resulting in hypotension, bronchoconstriction, and even convulsions. Additionally, research indicates that it is a teratogen. (Rida *et al.*, 2015)

Oral use of a combination preparation containing noscapine is used to lessen these effects. The primary codeine, noscapine, and opium alkaloids are comparable in terms of their antitussive duration of action, potency, and onset. Because noscapine is metabolized by the first pass, its bioavailability is comparatively low. By changing into o-demethylated metabolites and meconin, noscapine is rendered inactive. Meconin is one of noscapine's main urine metabolites. (Yao & Xiong, 2016)

4.6. 9-Octadecynoic Acid

9-octadecynoic acid (9-ODA), which has a triple bond at two points, stimulated PPARγ and caused fat buildup in 3T3-L1 fat cells, and this process relied on PPARγ. The way fatty acids, which consist of a triple bond, like 9-ODA, work as PPARγ activators is not well understood. 9-octadecynoic acid (9-ODA) functions as a PPARγ activator and may be useful in treating fibrosis and diabetes. (Nishino *et al.*, 2020)

In the in vitro antifungal testing, 9-octadecynoic acid shows that the positional triple bonds and chain lengths of the acetylenic acids were related to their antifungal activities. The potential of the antifungal compound 9-octadecynoic acid as a lead for the creation of novel therapies for topical fungal infections will receive special attention. (Ghimire, 2016)

5. Therapeutic Applications of Alkaloids in Cancer Pain and Cardiogenic Pulmonary Edema

5.1. Effect of Morphine in Treating Cancer-Related Pain

5.1.1. Historical Context and Global Awareness

For centuries, morphine has been utilized in various forms to alleviate pain in individuals with cancer. "Cancer Pain Relief," an international development initiative overseen by the WHO, is a global health policy document that addresses cancer pain (Fleckner *et al.*, 2023). The release of this document raised awareness of morphine's advantages throughout the world for managing cancer pain, but it took some time for other healthcare settings to adopt the routine morphine administration that was promoted in the UK's first hospices. This slower absorption was largely caused by concerns about the possibility of morphine tolerance and abuse. (Badshah *et al.*, 2024)

5.1.2. Concerns and Practical Challenges

The same worries that are commonplace worldwide about the usage of morphine in treating cancer-related pain have also surfaced at the micro-level. Anxiety is prevalent in patients, caregivers, and medical professionals, despite studies showing how well morphine works as an analgesic. The real-world effect is that patients may not follow their prescribed regimens or receive subpar or no morphine prescriptions at all. This leads to a poorer level of symptom control. (Rosenberg, 2022)

5.1.3. Research Synthesis and Methodological Advances

In order to start making sense of the discrepancy between morphine's efficacy and its practical application, research must be compiled in a manner that goes beyond some of the constraints of conventional systematic review techniques. Systematic reviews have come under fire for allegedly ignoring the relationship between research, practice, and policy despite their scientific approach to evidence synthesis.

As a result, there has been a push to include a wider range of evidence types in syntheses. It has been proposed

that integrating qualitative research may improve the clinical utility of trial results at the primary research level (Flemming *et al*., 2019). For systematic reviews, this might also be the case. Integrating qualitative and quantitative research at the synthesis level can improve the results of effectiveness studies by providing deeper insights into interventions and the best approaches for their implementation and management. (Noyes *et al*., 2019)

Numerous techniques have been developed for conducting syntheses of various research methods (Schick-Makaroff *et al*., 2016), which critical interpretive synthesis (CIS) is one method of addressing. A new approach to reviewing called CIS incorporates a qualitative tradition of inquiry along with the procedures of traditional systematic review methodology. Strong explanatory theories can be developed by synthesizing a variety of data sources using CIS. (Višić *et al*., 2024)

5.2*. Effect of Morphine in the Treatment of Acute Cardiogenic Pulmonary Edema*

5.2.1 Therapeutic Role and Mechanism

One medication that is frequently used to treat acute cardiogenic pulmonary edema is morphine (Ponikowski *et al*., 2016). By lowering preload and subsequently pulmonary capillary pressure, morphine helps in treating pulmonary edema. Additionally, it lessens the afterload somewhat. The opioid receptors mu and kappa are agonistically activated by the metabolite morphine-6-glucuronide of morphine at the cellular level.It is believed that side effects like addiction and respiratory system modification are related to the cation on mu receptors. (Witharana *et al*., 2022)

5.2.2. Guidelines and Risks

Both the National Institute for Health and Care Excellence and the European Society of Cardiology suggest that opioids should not be used regularly in AHF (acute heart failure). This is because of the risk of side effects that increase with dosage, such as slowed breathing, slow heart rate, nausea, and low blood pressure. (Dworzynski *et al*., 2014)

Morphine's prognostic benefits are still unknown, though; it's unclear if it only improves short-term symptoms or if it could potentially make things worse. Regarding a possible increased mortality risk in AHF patients getting morphine, there is conflicting evidence. Thus, the goal of this systematic review was to build on earlier meta-analyses by collecting and presenting the most recent information in an orderly manner. We wanted to find out if using morphine in acute cardiogenic pulmonary edema is linked to negative results for patients. (Gao *et al*., 2021; Gil *et al*., 2019)

At present, there's no data that supports the use of morphine for these patients. Therefore, current practice employs a therapeutic approach in which these critically ill patients are given a potentially harmful class of medication (Dominguez-Rodriguez & Abreu-Gonzalez, 2017). When treating patients with severe dyspnea, particularly those who have acute pulmonary edema, the ESC advises using morphine with caution. Similarly, the American College of Cardiology and American Heart Association state that morphine therapy should only be used in the palliative care of end-stage heart failure. (Kawaguchi *et al*., 2020)

5.2.3. Physiological Effects and Alternatives

Morphine is commonly used to treat anxiety and dyspnea. (López-Saca & Centeno, 2014) Increased vascular resistance is a result of endogenous catecholamine release in acute cardiogenic pulmonary edema (Dominguez-Rodriguez & Abreu-Gonzalez, 2017). Because of its vasodilatory effects, morphine causes a decrease in venous tone, which in turn lowers vascular return to the right side of the heart and, ultimately, lowers the output of the right ventricle (Caspi *et al*., 2019). Because of this, the weakened left ventricle may operate with less filling pressure. However, this may also result in hypotension and a reduction in cardiac output. A higher need for endotracheal intubations and ICU admissions can be connected to the decline in cardiac output. (Witharana *et al*., 2022)

The benefits of using morphine in acute cardiogenic pulmonary edema seem to be its anxiety-reducing effect and its ability to lower systemic vascular resistance. But it's possible that an alternative treatment, like benzodiazepines for anxiety, has comparable effects without as many side effects as morphine. (Witharana *et al*., 2022)

5.2.4. Drug Interactions and Ongoing Research

The way that morphine interacts with other drugs can also contribute to its negative effects. Antiplatelets like ticagrelor, clopidogrel, and prasugrel showed delayed activity when combined with morphine. Additionally, there is proof that morphine lowers heart rate and, in turn, cardiac output. 19 This may result in ischemia, cardiogenic shock, and a decrease in myocardial perfusion. Patients with ischemic heart disease, who already have a heartfailure risk, might die because of these effects on the heart. (Agewall, 2017)

Morphine effects are still debatable. The multi-center prospective randomized trial, Midazolam versus Morphine in Acute Pulmonary Oedema (MIMO), evaluates the safety of morphine in treating acute cardiogenic pulmonary oedema in an effort to fill up the knowledge gaps that currently exist. (Dominguez-Rodriguez *et al*., 2017)

6. Conclusion

Papaver somniferum L. (opium poppy) is a key medicinal plant, with morphine effectively managing severe cancer pain via mu-opioid receptor activation. However, concerns about tolerance and addiction lead to under-prescription, affecting symptom control. Integrating diverse evidence is crucial to improve pain management practices. In acute cardiogenic pulmonary edema (ACPE), morphine reduces preload, afterload, and anxiety, but risks like respiratory depression and drug interactions, coupled with unclear prognostic benefits, limit its use.Other alkaloids—codeine, papaverine, and noscapine—enhance therapeutic versatility, but risks like addiction and pruritus require cautious use and further research, such as esketamine for itching. Morphine remains vital for cancer pain but demands caution in ACPE. In conclusion, while *Papaver somniferum*-derived alkaloids, especially morphine, remain indispensable in oncology, their utility in cardiovascular contexts warrants greater scrutiny, and alternative therapies should be prioritized in light of emerging clinical evidence.

7. Future Perspective

The future of Papaver somniferum alkaloids lies in optimizing their therapeutic applications through precision medicine, safer delivery systems, and alternative therapies, while addressing regulatory and safety challenges. Continued research into both alkaloid and non-alkaloid constituents, coupled with global collaboration and innovative biotechnological approaches, will enhance their clinical utility and mitigate risks, particularly in the contexts of cancer pain and ACPE management.

Abbreviations

ACPE: Acute Cardiogenic Pulmonary Edema; **BIAs:** Benzylisoquinoline Alkaloids; **CNS:** Central Nervous System; **CIS:** Critical Interpretive Synthesis; **AHF:** Acute Heart Failure; **M3G:** Morphine-3-glucuronide; **9-ODA:** 9-Octadecynoic Acid; **PPARγ:** Peroxisome Proliferator-Activated Receptor Gamma

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Authorship Contribution

Karan Thakur: Drafted the introduction, body, and conclusion sections of the manuscript; Shivam Thakur: Drafted the introduction, body, and conclusion sections of the manuscript; Abhay Sharma: Organized content into logical sections or themes for coherent presentation; Khemender Lidoo: Organized content into logical sections or themes for coherent presentation; Om Kumar: Organized content into logical sections or themes for coherent presentation; Scindia Kohli: Contributed to drafting and assessing the quality and reliability of reviewed studies; Rupinder Kaur: Highlighted key insights and implications derived from the review; Amit Sharma: Manuscript review and editing; Sarita Jangra: Conceptualization, final editing, corresponding author.

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Conflict of Interest

The authors declare no conflicts of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

Ethical Statement

This review article, adheres to the Declaration of Helsinki. It synthesizes data from peer-reviewed studies (2015–2025) from PubMed, Scopus, and Web of Science, with no primary data collection. The authors declare no conflicts of interest. All sources are properly cited, and the review was conducted with academic integrity, free from bias or discrimination.

References

Agewall, S. (2017). Morphine in acute heart failure. *Journal of Thoracic Disease, 9*(7), 1851. https://doi.org/10.21037/jtd.2017.06.126

Badshah, I., Anwar, M., Murtaza, B., & Khan, M. I. (2024). Molecular mechanisms of morphine tolerance and dependence; novel insights and future perspectives. *Molecular and Cellular Biochemistry, 479*(6), 1457–1485. https://doi.org/10.1007/s11010-023-04909-0

Baser, K. H. C., & Arslan, N. (2014). Opium poppy (Papaver somniferum). In Z. Yaniv & N. Dudai (Eds.), *Medicinal and aromatic plants of the Middle-East* (pp. 305–332). Springer Netherlands. https://doi.org/10.1007/978-94-017-9276-9_17

Beaudoin, G. A., & Facchini, P. J. (2014). Benzylisoquinoline alkaloid biosynthesis in opium poppy. *Planta, 240*, 19–32. https://doi.org/10.1007/s00425-014-2056-8

Butnariu, M., Quispe, C., Herrera-Bravo, J., Pentea, M., Sarac, I., Küşümler, A. S., Özçelik, B., Painuli, S., Semwal, P., Imran, M., Gondal, T. A., Emamzadeh-Yazdi, S., Lapava, N., Yousaf, Z., Kumar, M., Eid, A. H., Al-Dhaheri, Y., Suleria, H. A. R., Del Mar Contreras, M., & Cho, W. C. (2022). *Papaver* plants: Current insights on phytochemical and nutritional composition along with biotechnological applications. *Oxidative Medicine and Cellular Longevity, 2022*, 2041769. https://doi.org/10.1155/2022/2041769

Carlin, M. G., Dean, J. R., & Ames, J. M. (2020). Opium alkaloids in harvested and thermally processed poppy seeds. *Frontiers in Chemistry, 8*, 737. https://doi.org/10.3389/fchem.2020.00737

Caspi, O., Naami, R., Halfin, E., & Aronson, D. (2019). Adverse dose-dependent effects of morphine therapy in acute heart failure. *International Journal of Cardiology, 293*, 131–136. https://doi.org/10.1016/j.ijcard.2019.06.058

Celik, I., Camci, H., Kose, A., Kosar, F. C., Doganlar, S., & Frary, A. (2016). Molecular genetic diversity and association mapping of morphine content and agronomic traits in Turkish opium poppy (Papaver somniferum) germplasm. *Molecular Breeding, 36*, 1–13. https://doi.org/10.1007/s11033-016-3967-9

Chain, E. P., Knutsen, H. K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B., Ceccatelli, S., Cottrill, B., Dinovi, M., & Edler, L. (2018). Update of the scientific opinion on opium alkaloids in poppy seeds. *EFSA Journal, 16*(5), e05243. https://doi.org/10.2903/j.efsa.2018.5243

Demirkapu, M. J., & Yananli, H. R. (2020). Opium alkaloids. In *Bioactive compounds in nutraceutical and functional food for good human health*.

Di Sotto, A., Valipour, M., Azari, A., Di Giacomo, S., & Irannejad, H. (2023). Benzoindolizidine alkaloids tylophorine and lycorine and their analogues with antiviral, anti-inflammatory, and anticancer properties: Promises and challenges. *Biomedicines, 11*(10), 2619. https://doi.org/10.3390/biomedicines11102619

Dominguez-Rodriguez, A., & Abreu-Gonzalez, P. (2017). A critical appraisal of the morphine in the acute pulmonary edema: Real or real uncertain? *Journal of Thoracic Disease, 9*(7), 1802. https://doi.org/10.21037/jtd.2017.06.88

Dominguez-Rodriguez, A., Burillo-Putze, G., Garcia-Saiz, M. d. M., Aldea-Perona, A., Harmand, M. G.-C., Miro, O., Abreu-Gonzalez, P., & Piñera Salmeron. (2017). Study design and rationale of "a multicenter, open-labeled, randomized controlled trial comparing midazolam versus morphine in acute pulmonary edema": MIMO trial. *Cardiovascular Drugs and Therapy, 31*, 209–213. https://doi.org/10.1007/s10557-017-6720-3

Dworzynski, K., Roberts, E., Ludman, A., & Mant, J. (2014). Diagnosing and managing acute heart failure in adults: Summary of NICE guidance. *BMJ, 349*. https://doi.org/10.1136/bmj.g5650

Fleckner, J., Pettus, K., Vallath, N., & Pastrana, T. (2023). Systematic review on barriers to access opioid analgesics for cancer pain management from the health worker perspective. *Journal of Pain & Palliative Care Pharmacotherapy, 37*(4), 324–335. https://doi.org/10.1080/15360288.2023.2241630

Flemming, K., Booth, A., Garside, R., Tunçalp, Ö., & Noyes, J. (2019). Qualitative evidence synthesis for complex interventions and guideline development: Clarification of the purpose, designs and relevant methods. *BMJ Global Health, 4*(Suppl 1). https://doi.org/10.1136/bmjgh-2018-001184

Gao, D., David, C., Rosa, M. M., Costa, J., Pinto, F. J., & Caldeira, D. (2021). The risk of mortality associated with opioid use in patients with acute heart failure: Systematic review and meta-analysis. *Journal of Cardiovascular Pharmacology, 77*(2), 123–129. https://doi.org/10.1097/FJC.0000000000000950

Ghimire, G. P. (2016). Bioactive compounds and biological activities of some medicinal plants from central Nepal.

Gil, V., Domínguez-Rodríguez, A., Masip, J., Peacock, W. F., & Miró, Ò. (2019). Morphine use in the treatment of acute cardiogenic pulmonary edema and its effects on patient outcome: A systematic review. *Current Heart Failure Reports, 16*, 81–88. https://doi.org/10.1007/s11897-019-00428-5

Gossel, T. A. (2018). *Principles of clinical toxicology*. CRC Press.

Guthrie, S. K., & Teter, C. (2016). Opioid analgesics. In *Applied clinical pharmacokinetics and pharmacodynamics of psychopharmacological agents* (pp. 267–301). Springer.

György, Z., Alam, S., Priyanka, P., & Zámboriné Németh, É. (2022). Genetic diversity and relationships of opium poppy accessions based on SSR markers. *Agriculture, 12*(9), 1343. https://doi.org/10.3390/agriculture12091343

Hayat, M. T., Hameed, U., & Zia-Ul-Haq, M. (2023). Opium poppy. In *Essentials of medicinal and aromatic crops* (pp. 935–964). Springer. https://doi.org/10.3390/agriculture12091343

Herman, T., Cascella, M., & Muzio, M. R. (2024). Mu receptors. *StatPearls*.

Hong, U. V. T., Tamiru-Oli, M., Hurgobin, B., Okey, C. R., Abreu, A. R., & Lewsey, M. G. (2022). Insights into opium poppy (Papaver spp.) genetic diversity from genotyping-by-sequencing analysis. *Scientific Reports, 12*(1), 111. https://doi.org/10.1038/s41598-021-03986-1

Jesus, A., Bonhomme, V., Evin, A., Ivorra, S., Soteras, R., Salavert, A., Antolín, F., &Bouby, L. (2021). A morphometric approach to track opium poppy domestication. *Scientific Reports, 11*, 9778. https://doi.org/10.1038/s41598-021-88945-0

Kawaguchi, J., Hamatani, Y., Hirayama, A., Nishimura, K., Nakai, E., Nakamura, E., Miyata, M., Kawano, Y., Takada, Y., & Anchi, Y. (2020). Experience of morphine therapy for refractory dyspnea as palliative care in advanced heart failure patients. *Journal of Cardiology, 75*(6), 682–688. https://doi.org/10.1016/j.jjcc.2019.12.012

Kumaravel, S., Muthukumaran, P., & Thomas, N. (2019). Phytochemical, GC-MS and FT-IR analysis of *Papaver somniferum*. *Journal of Pharmaceutical and Biological Sciences, 7*, 1–8. https://doi.org/10.18231/j.jpbs.2019.001

Labanca, F., Ovesná, J., & Milella, L. (2018). *Papaver somniferum* L. taxonomy, uses and new insight in poppy alkaloid pathways. *Phytochemistry Reviews, 17*(4), 853–871. https://doi.org/10.1007/s11101-018-9560-0

Lahiri, R., Lal, R., Srivastava, N., & Shanker, K. (2018). Genetic variability and diversity in Indian germplasm of opium poppy (*Papaver somniferum* L.). *Journal of Applied Research on Medicinal and Aromatic Plants, 8*, 41–46. https://doi.org/10.1016/j.jarmap.2017.11.002

López-Saca, J. M., & Centeno, C. (2014). Opioids prescription for symptoms relief and the impact on respiratory function: Updated evidence. *Current Opinion in Supportive and Palliative Care, 8*(4), 383–390. https://doi.org/10.1097/SPC.0000000000000096

Masihuddin, M., Jafri, M., Siddiqui, A., & Chaudhary, S. (2018). Traditional uses, phytochemistry and pharmacological activities of *Papaver somniferum* with special reference to Unani medicine: An updated review. *Journal of Drug Delivery and Therapeutics, 8*(5-s), 110–114. https://doi.org/10.7324/JDDT.2018.855110

Nishino, K., Uesugi, H., Hirasawa, A., Ohtera, A., Miyamae, Y., Neffati, M., Isoda, H., Kambe, T., Masuda, S., & Irie, K. (2020). Stimulation of insulin secretion by acetylenic fatty acids in insulinoma MIN6 cells through FFAR1. *Biochemical and Biophysical Research Communications, 522*(1), 68–73. https://doi.org/10.1016/j.bbrc.2019.10.155

Noyes, J., Booth, A., Moore, G., Flemming, K., Tunçalp, Ö., & Shakibazadeh, E. (2019). Synthesising quantitative and qualitative evidence to inform guidelines on complex interventions: Clarifying the purposes, designs and outlining some methods. *BMJ Global Health, 4*(Suppl 1), e000893. https://doi.org/10.1136/bmjgh-2018-000893

Olsen, Y., & Sharfstein, J. M. (2019). *The opioid epidemic: What everyone needs to know*. Oxford University Press.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., Falk, V., González-Juanatey, J. R., Harjola, V.-P., & Jankowska, E. A. (2016). 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Kardiologia Polska (Polish Heart Journal), 74*(10), 1037–1147. https://doi.org/10.5603/KP.2016.0140

Rida, P. C., LiVecche, D., Ogden, A., Zhou, J., & Aneja, R. (2015). The noscapine chronicle: A pharmaco-historic biography of the opiate alkaloid family and its clinical applications. *Medicinal Research Reviews, 35*(5), 1072–1096. https://doi.org/10.1002/med.21349

Rosenberg, J. (2022). 7th public health palliative care. *Practice, 16*, 1–119. https://doi.org/10.1177/26323524221119941

Salavert, A., Zazzo, A., & Martin, L. (2020). Direct dating reveals the early history of opium poppy in western Europe. *Scientific Reports, 10*, 20263. https://doi.org/10.1038/s41598-020-76930-1

Saunders, J. A., Pedroni, M. J., Penrose, L. D., & Fist, A. J. (2001). AFLP analysis of opium poppy. *Crop Science, 41*(5), 1596–1601. https://doi.org/10.2135/cropsci2001.4151596x

Schick-Makaroff, K., MacDonald, M., Plummer, M., Burgess, J., & Neander, W. (2016). What synthesis methodology should I use? A review and analysis of approaches to research synthesis. *AIMS Public Health, 3*(1), 172. https://doi.org/10.3934/publichealth.2016.1.172

Shimoji, K., & Fujioka, H. (2020). Pharmacology of analgesics. In *Chronic Pain Management in General and Hospital Practice* (pp. 55–86). Springer. https://doi.org/10.1007/978-981-15-2933-7_5

Srivastava, A., Gupta, S., Shanker, K., Gupta, N., Gupta, A. K., & Lal, R. (2020). Genetic diversity in Indian poppy (*Papaver somniferum* L.) germplasm using multivariate and SCoT marker analyses. *Industrial Crops and Products, 144*, 112050. https://doi.org/10.1016/j.indcrop.2019.112050

Svoboda, P., Vašek, J., Vejl, P., & Ovesná, J. (2020). Genetic features of Czech blue poppy (*Papaver somniferum* L.) revealed by DNA polymorphism. *Czech Journal of Food Sciences, 38*(3), 198–202. https://doi.org/10.17221/26/2020-CJFS

Tamiru-Oli, M., Premaratna, S. D., Gendall, A. R., & Lewsey, M. G. (2018). Biochemistry, genetics, and genomics of opium poppy (*Papaver somniferum*) for crop improvement. *Annual Plant Reviews Online*, 1177–1219.

Troy, D. B. (2005). *Remington: The science and practice of pharmacy*.

Ueda, M., Hirayama, Y., Ogawa, H., Nomura, T., Terashi, H., & Sakakibara, S. (2023). Vasodilating effects of antispasmodic agents and their cytotoxicity in vascular smooth muscle cells and endothelial cells—Potential application in microsurgery. *International Journal of Molecular Sciences, 24*(13), 10850. https://doi.org/10.3390/ijms241310850

Višić, M., Balenović, A., & Mesarić, J. (2024). Synthesising research findings–Methodological guidelines for conducting the critical interpretive synthesis method. *Teorija in Praksa, 61*(4). https://doi.org/10.51936/tip.61.4.909

Witharana, T. N., Baral, R., & Vassiliou, V. S. (2022). Impact of morphine use in acute cardiogenic pulmonary oedema on mortality outcomes: A systematic review and meta-analysis. *Therapeutic Advances in Cardiovascular Disease, 16*, 17539447221087587. https://doi.org/10.1177/17539447221087587

Wolf, C. E., Pierce, K. L., Goldfine, B. L., Nanco, C. R., Poklis, J. L., & Korzun, W. J. (2019). Using papaverine and its metabolites, 6-desmethyl papaverine and 4′,6-didesmethyl papaverine as biomarkers to improve the detection time of heroin use. *Journal of Analytical Toxicology, 43*(8), 600–606. https://doi.org/10.1093/jat/bkz042

Yao, Y., & Xiong, Y. (2016). Metabolic pathway profiling of the derivative of important herbal component noscapine. *European Journal of Drug Metabolism and Pharmacokinetics, 41*(1), 27–32. https://doi.org/10.1007/s13318-014-0232-7

Zohary, D., Hopf, M., & Weiss, E. (2012). *Domestication of plants in the Old World: The origin and spread of domesticated plants in Southwest Asia, Europe, and the Mediterranean Basin*. Oxford University Press.