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RESEARCH ARTICLE

Occurence of opium alkaloids in food – threads and future prospects

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Abstract

Opium poppy is a widely known plant with wide use in both medicine and the food industry. Substances present on the surface of dry poppy seeds and poppy-based products belong to the group of opium alkaloids, which include, among others: morphine and codeine. Both of these compounds, like other opiates, are used in the pharmaceutical industry due to their proven analgesic properties. The presence of these substances in food products poses a risk to the health of consumers, therefore changes have been introduced in the current Regulation (EU) 2023/915 regarding the permissible levels of morphine and codeine in poppy seed products. Numerous studies conducted over recent years have shown that legal limits have been exceeded, which may be associated with negative health effects for consumers. This paper presents the current state of knowledge on the occurrence of opium alkaloids and the possible effects of exposure to these substances in humans, as well as an analysis of the risk caused by the intake of these substances from food.

KEYWORDS
opium alkaloids, opium poppy, morphine, codeine, toxicity

INTRODUCTION

Medical Poppy (Latin: Papaver somniferum L.) is a species with a wide range of applications in both the pharmaceutical and food industries. In the pharmaceutical industry, substances contained in latex are utilized. These compounds belong to the group of opium alkaloids (OAs) and are used in medicine as painkillers or to inhibit mucus secretion from the lower respiratory tract [Butnariu et al. 2022]. While their significance in the pharmaceutical industry is crucial, in the food industry, the presence of opium alkaloids is limited by Regulation (EU) 2023/915 concerning food contaminants. Unfortunately, recent literature data indicates increasing contamination of poppy seeds with these substances [Lopez et al. 2018; Carlin et al. 2020; Casado-Hidalgo et al. 2021]. The seeds themselves do not contain opiates; contamination occurs mainly due to improper harvesting practices leading to latex contamination of the seeds, which contains alkaloids [Casado-Hidalgo et al. 2021].

Opium is a dried milk obtained from poppy seed pods. Both immature poppy heads and stems, roots, and leaves are rich in latex. The total opium alkaloid content in poppy plants depends on several factors: species, climatic conditions, or the cultivation region [Eisenreich et al. 2020]. Latex is a source of benzylisoquinoline alkaloids (BIAs), which accumulate in specialized secretory cells (laticifers) [Ozber et al. 2022]. Opium alkaloids have been classified into two chemical groups, i.e., phenanthrenes (morphine, codeine, oripavine, or thebaine) and benzylisoquinolines (papaverine and noscapine) [Eisenreich et al. 2020]. Additionally, there is a division into three main classes: natural, synthetic, and semi-synthetic. Naturally occurring compounds include morphine, codeine, thebaine, papaverine, oripavine, and noscapine. Among synthetic and semi-synthetic opiates, heroin (diacetylmorphine), methadone, fentanyl, oxycodone (the active ingredient in OxyContin), and hydrocodone (the active ingredient in Lortab, Norco, Vicodin) can be distinguished [Vadhel et al. 2023]. In ancient times, opium was collected for medicinal as well as recreational purposes. In antiquity, the first methods of extracting alkaloids were developed mainly due to their analgesic, anti-inflammatory, relaxing properties, and alleviating neurological disorders [Vadhel et al. 2023]. Nowadays, numerous studies indicate the negative impact of opiates on cognitive brain functions

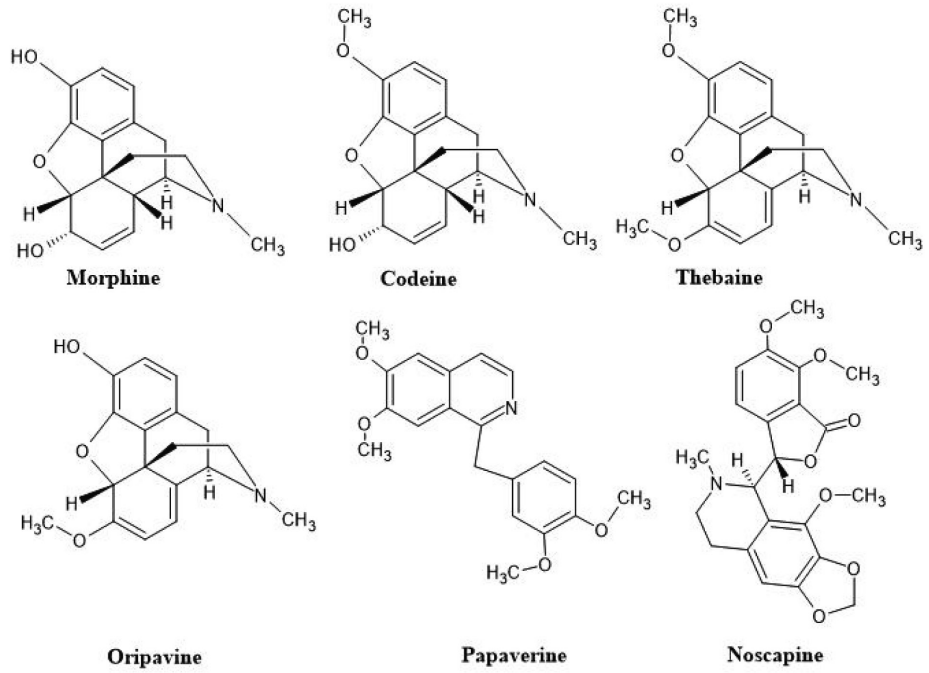

Figure 1.
Structures of opium alkaloids.

through changes in its molecular and neuronal structures. Opiate use leads to neuroadaptation, which consequently leads to changes in emotional and pain centers. Long-term use causes changes in the structure and functioning of brain areas responsible for motivation, reward, or decision-making [Kosten et al. 2002, Vadhel et al. 2023]. Dysfunction of these areas leads to cognitive impairment, which in turn contributes to the development of mental disorders, such as depression or anxiety. Additionally, these changes lead to hypersensitivity, and consequently, an increased risk of addiction to these substances and compulsive behaviors associated with a strong need to take the drug. Besides the neurological and psychological aspects of opiate use, in recent years, there has been increasing attention to the possible association of cancer occurrence in individuals exposed to opiates [Vadhel et al. 2023].

Consumption of products contaminated with opium alkaloids carries significant health risks, especially for children, the elderly, or pregnant women [Casado-Hidalgo et al. 2021]. Many countries in Europe and worldwide have taken measures to limit the risk of contamination of poppy-based products with alkaloids. These measures include the use of low-opiate poppy varieties and the establishment of maximum limits for morphine and codeine in food products. For these reasons, the cultivation of medicinal poppy is illegal or restricted by legal regulations allowing the cultivation of only specific species [Cerven et al. 2023]. Currently, the cultivation of Papaver somniferum L. for food and pharmaceutical purposes is permitted in Poland, Russia, Iran, Canada, Spain, Romania, Slovakia, France, Hungary, Turkey, the Czech Republic, the Netherlands, Australia, Central and South America [Ngernsaengsaruay et al. 2023]. However, it should be noted that in some of these countries, only low-morphine varieties are allowed for food purposes (Czech Republic), while in others, varieties useful in the pharmaceutical industry are also permitted (Spain, France, Australia) [Ngernsaengsaruay et al. 2023].

The aim of this work is to update the state of knowledge on the occurrence of opium alkaloids in food, characterize the toxicity of individual compounds, assess the risk associated with the consumption of food contaminated with them, and indicate future perspectives to minimize this risk.

1. Characterization and Toxicity of Opium Alkaloids

Opium alkaloids were first isolated and described in 1803 by the Parisian scientist François Derosne. The term "alkaloids" was coined by Karl Meissner in 1818 and remains in use to this day [Presley et al. 2018, Demirkapu, Yananli 2020]. The activity of these compounds on the μ-, δ-, and κ-opioid receptors, which are distributed in peripheral tissues and the central nervous system, causes a range of neurophysiological effects such as minimizing pain sensations, relaxation, euphoria, drowsiness, respiratory depression, or nausea. Stimulation of these receptors also results in pupil constriction, hypotension, or short-term impairment of the physiological function of the digestive and excretory systems [Demirkapu, Yananli 2020, Furst et al. 2020, Dhaliwal, Gupta 2023]. The addictive mechanism of opioids on the central nervous system is still not fully understood. However, it is known that the nervous system undergoes significant biochemical and morphological changes [Przewłocki, 2017]. Compounds in the opium alkaloid group are described in detail and graphically presented below (Figure 1).

Morphine

Morphine in its pure form was first isolated, identified, and thoroughly studied by Friedrich Sertürner between 1803 and 1817 [Krishnamurti, Rao 2016]. Initial experiments showed that morphine alleviates pain and induces a feeling of euphoria. However, it also has side effects, including nausea, constipation, and vomiting, as well as a strong potential for addiction [Kaboudin, Sohrabi 2021]. According to the European Food Safety Authority (EFSA) in 2018, morphine is intensely absorbed by the digestive system and then distributed throughout the body, with the brain being the primary site of absorption [EFSA 2018]. Long-term use of morphine develops tolerance and strong physical and psychological dependence. Its action on opioid receptors results in a feeling of euphoria, reduced pain sensations, and sedation [EFSA 2018]. According to Dasgupta [2019], morphine constitutes about 4–21% of opium [Dasgupta 2019]. Considering that codeine, which is metabolized into morphine, does not exhibit carcinogenic activity, it can be assumed that morphine also does not have such an effect [EFSA 2018]. According to numerous literature data, morphine is

one of the most frequently occurring alkaloids in poppy products, usually in alarmingly high doses exceeding 20 mg/kg, and in some cases reaching values above 200 mg/kg [Sproll et al. 2006, Lopez et al. 2018, Shetge et al. 2020].

Codeine

Codeine is the second substance after morphine whose anesthetic properties have been utilized in medicine as one of the most commonly used analgesic preparations to this day [Kaboudin, Sohrabi 2021]. Like morphine, it exhibits antagonistic effects on α-, μ-, and K-opioid receptors involved in the body's pain response. Long-term use of codeine leads to the development of tolerance to its analgesic effects, and consequently to addiction, requiring the intake of increasingly larger doses [Powers et al. 2017]. When administered orally, codeine is rapidly absorbed into the digestive system. Similar to morphine, it crosses the placental barrier and enters the fetal circulation [EFSA 2018]. It is metabolized mainly in the liver, where it is converted to morphine, codeine-6-glucuronide (C6G), and norcodeine. It has been shown that the maximum conversion of codeine to morphine does not exceed 20%. Regarding toxicity assessment, based on available data, it has been estimated that codeine does not exhibit carcinogenic, neurotoxic, genotoxic, or teratogenic effects [EFSA 2018]. The proportion of codeine in opium ranges between 0.8–2.5% [Dasgupta 2019].

Thebaine

Structurally, thebaine is similar to morphine and codeine, possessing the characteristic morphinan D-ring containing nitrogen (Figure 1) and serving as a key intermediate compound during the biosynthesis of morphine [Abarna et al. 2023]. The proportion of thebaine in opium ranges between 0.5–2.0% [Dasgupta 2019]. Currently, there is limited data on the toxicity and toxicokinetics of thebaine, but according to EFSA, it is more toxic than morphine [EFSA 2018]. This opinion is based on studies indicating higher toxicity of thebaine compared to morphine, supported by the determination of the lethal dose (LD50 – the dose of a substance at which 50% of the tested animals die under specific experimental conditions) of thebaine in various animal species [EFSA 2018]. The LD50 of thebaine administered via gastric intubation was 54 mg/kg body weight (bw) or 114 mg/kg bw in mice and rats, respectively. These values were compared to the LD50 values for morphine (LD50 = 524 mg/kg bw in mice; 335 mg/kg bw in rats via gastric administration), showing that the LD50 doses for thebaine are significantly lower compared to morphine [EFSA 2018]. Thebaine mediates the stimulation of the central nervous system, resulting in increased irritability and motor excitation, as confirmed in numerous animal studies [Navarro, Elliott 1971; Misra et al. 1973]. Currently, there is limited data regarding the impact of thebaine on human health. This alkaloid is not used for therapeutic purposes, but it can be present in poppy seeds along with other opiate compounds. Thebaine is a precursor for the production of semi-synthetic opiates, including pharmacologically used ones such as oxycodone, oxymorphone, and buprenorphine, which are administered as analgesics in cancer patients [Eisenreich et al. 2020; Kaboudin, Sohrabi 2021].

Oripavine

Oripavine, like codeine and morphine, also exhibits antagonistic effects on the μ-opioid receptor, but its activity is greater than that of codeine and less than that of morphine. There is insufficient data on the toxicity of oripavine to determine its LD50 dose for oral administration. However, based on studies conducted on rats with non-oral administration, it is considered to be more toxic compared to morphine [EFSA 2018].

Noscapine

The proportion of noscapine in opium ranges from 1–10%. Initially, noscapine was considered useless by researchers, but gradually its therapeutic properties were discovered, such as its antitussive (cough suppressant) effect in 1930 and its anti-stroke properties in 2003 [Kaboudin and Sohrabi 2021]. Noscapine exerts minimal effects on the central nervous system and does not stimulate euphoric effects. With virtually no severe side effects or addictive potential, noscapine serves as an alternative to codeine in treating cough [Rahmanian-Devin et al. 2021, Kaboudin, Sohrabi 2021]. Additionally, this compound may exhibit anticancer properties [Dasgupta 2019]. Its inhibitory activity against the growth of certain cancers, including lung and colon tumors, has been confirmed in numerous studies [Tian et al. 2020, Islam et al. 2022]. However, it should be noted that noscapine does not exhibit analgesic effects, and its use in medicine is primarily as a cough suppressant.

Papaverine

Papaverine is an alkaloid present in opium at levels of 0.5–1.0%. It has been known for centuries for its smooth muscle relaxant properties and its ability to enhance the analgesic effects of weaker over-the-counter medications, such as aspirin [EFSA 2018, Kaboudin, Sohrabi 2021, Abarna et al. 2023]. Papaverine has been used in medicine for over a century. Its side effects are considered minor and include nausea, vomiting, headaches, and drowsiness. Although this substance is not subject to international control, there is a possibility that long-term administration could lead to addiction. Therefore, its presence is discouraged in poppy seeds intended for consumption as a preventive measure [Kaboudin, Sohrabi 2021].

2. Presence of Opium Alkaloids in Poppy Seeds and Poppy-Based Products

Results from numerous analyses in recent years indicate that the contamination of poppy seeds with opium alkaloids, including morphine, codeine, and thebaine, is an ongoing issue, and corrective measures should be taken (Table 1). In October 2011, the EFSA Panel on Contaminants in the Food Chain (CONTAM) issued an opinion on the risk posed by the presence of opium alkaloids in poppy seeds and poppy-based products, such as poppy seed pastes, bakery products, and confectionery.

Due to the confirmed presence of these substances in significant amounts in the mentioned products, it was determined that the risk assessment could be based on the exposure of the average consumer to morphine ingested through diet. Consequently, an Acute Reference Dose (ARfD) was estimated at 10 μg/kg body weight [EFSA 2018]. According to the current Commission Regulation (EU) 2023/91, the maximum allowable content of morphine (sum of morphine and codeine content multiplied by a factor of 0.2, as codeine is a precursor to morphine) in whole, ground, or milled seeds should not exceed 20 mg/kg of the product.

Table 1. Content of opium alkaloids in poppy seeds and poppy

Type of alcaloids	Material	Number of samples	Min–Max [mg/kg]	References
Morphine	Poppy seeds	6	21–210	Montgomery et al. 2020
	Poppy seeds	13	30,55–57,94	Casado-Hidalgo et al. 2021
	Poppy seeds	41	0,2–241,0	Lopez et al. 2018
	Poppy seeds	15	3,6–261,0	Shetge et al. 2020
	Poppy seeds	83	<1–270	Sproll et al. 2006
	Poppy seeds	29	0,022–0,029	Guo et al. 2013
	Poppy paste	3	1,9–4,0	Ozbunar et al. 2019
	Herbal tea	2	10,4–31,5	Van Thuyne et al. 2003
	Bakery mix	83	<0,3–4,0	Sproll et al. 2006
	Poppy seeds	8	0,90–12,58	Carlin et al. 2020
Codeine	Poppy seeds	8	0,39–6,14	Carlin et al. 2020
	Poppy seeds	83	<0,3–56,0	Sproll et al. 2006
	Poppy seeds	13	4,46–10,88	Casado-Hidalgo et al. 2021
	Poppy seeds	41	<0,1–348,0	Lopez et al. 2018
Thebaine	Poppy seeds	13	7,59–21,03	Casado-Hidalgo et al. 2021
	Poppy seeds	8	0,37–37,22	Carlin et al. 2020
	Poppy seeds	41	<0,1–106,0	Lopez et al. 2018
Oripavine	Poppy seeds	13	5,3–9,1	Casado-Hidalgo et al. 2021
Papaverine	Poppy seeds	13	5,17–12,06	Casado-Hidalgo et al. 2021
	Poppy seeds	41	< 0,1–3,8	Lopez et al. 2018
Noscapine	Poppy seeds	13	8,0–39,7	Casado-Hidalgo et al. 2021
	Poppy seeds	8	0,30–6,83	Carlin et al. 2020
	Poppy seeds	41	0,1–6,0	Lopez et al. 2018

3. Prospects for minimizing risks associated with opium alkaloid contamination and consumption

Recent literature from the last decade indicates that contamination of poppy seeds with opium alkaloids, especially morphine and codeine, often significantly exceeds permissible levels. The presence of thebaine is particularly concerning due to its higher toxicity compared to morphine. Lopez et al. [2018] reported disturbingly high levels of morphine, codeine, and thebaine ranging from 0.2–241.0 mg/kg, <0.1–348.0 mg/kg, and <0.1–106.0 mg/kg, respectively. These values far exceed the maximum limits established by Commission Regulation (EU) 2023/91. Similarly, other studies by Shetge et al. [2020], Montgomery et al. [2020], and Sproll et al. [2007] also found morphine levels in poppy seeds significantly exceeding permissible limits multiple times over. Given morphine's significant impact on the central nervous system and its addictive potential, its presence in consumer-accessible poppy products poses a substantial health risk.

Ozbunar et al. [2019] conducted tests on healthy adults before and after consuming commercially available poppy paste, revealing opiates (morphine, codeine, and thebaine) in urine post-consumption. Additional studies confirmed that prior consumption of poppy products can affect drug test results [Casella et al. 1997, Samano et al. 2015], with morphine and codeine detected in saliva and urine up to 6 hours and 1.5 hours post-consumption, respectively. Despite lower typical levels, codeine and thebaine content in poppy seeds are significantly lower than morphine. However, their cumulative presence raises concerns given regulatory standards focusing on morphine and codeine levels. Although thebaine content lacks specific limits, its presence at levels of 0.37–37.22 mg/kg [Carlin et al. 2020] poses potential risks to consumers of poppy-based products due to its likely higher toxicity compared to other alkaloids.

Other alkaloids are typically absent or occur at much lower levels in poppy seeds and poppy-based products compared to morphine, codeine, and thebaine, except for noscapine, which was found at levels of 8.0–39.7 mg/kg by Casado-Hidalgo et al. [2021]. Noscapine, however, is considered safe and potentially beneficial due to its anticancer properties.

4. Mitigation Measures for Opium Alkaloid Contamination in Poppy Seeds and Derived Products

Given the current level of contamination of poppy seeds with opium alkaloids, particular caution is recommended during all stages of distribution, including harvesting, transport, storage, and technological processes during production. According to Commission Recommendation (EU) 2014/662, appropriate methods of pre-processing and processing should be applied to reduce the content of these substances in seeds and derived products. It is recommended, first and foremost, that poppy seeds intended for food purposes be harvested using specialized grain combines whose components are adapted for harvesting small seeds without damaging their structure, thereby preventing penetration of alkaloids into the interior.

After harvesting, seeds should undergo conditioning and cleaning using an aspirator to remove dust particles (from straw and bag walls), which can contribute to increased alkaloid content on the surface. The storage process itself also requires specific humidity and ventilation conditions.

The Recommendation also specifies parameters for individual technological treatments that should be implemented in the pre-processing and proper processing of poppy seeds. The effectiveness of properly conducted treatments can reach up to 90–100% depending on their combination [Commission Recommendation (EU) 2014/662]. Based on studies conducted, Sproll et al. [2007] suggested washing seeds (60°C, 2 min) and drying (40°C, 2 h), followed by grinding as effective methods to prevent microbiological contamination. The thermal processing should be carried out at the highest possible temperature (200°C). The use of this method reduces alkaloid content and improves the overall organoleptic quality of the product [Sproll et al. 2007]. In more recent studies, Shetge et al. [2020] indicated that baking at high temperatures alone does not achieve significant reduction in opium alkaloids in poppy seeds.

To increase degradation of morphine, codeine, and thebaine, thermal processing should be extended at maximum temperature (200°C) and/or preceded by a washing process. Researchers demonstrated that applying these procedures can achieve a 50–80% reduction depending on whether the baking process was preceded by washing.

Another method was proposed in the study by Casado-Hidalgo et al. [2023]. They examined the impact of fermentation processes on reducing opium alkaloid levels in milk-based fermented beverages enriched with poppy seeds. Morphine, noscapine, and papaverine were detected in the samples tested but below the limit of quantitation (LOQ). The fermentation process itself reduced opioid content by 33–80% within the first hours of the process. The results obtained by Casado-Hidalgo et al. [2023] provide new perspectives for developing effective methods to reduce opium compounds in poppy seeds. However, this issue should be further explored in future studies to determine the most beneficial parameters of the fermentation process conducive to reducing morphine and other alkaloids, as well as evaluating which strains of lactic acid bacteria (LAB) exhibit the greatest potential for degrading these compounds.

CONCLUSION

Current research indicates dangerously high levels of various opium alkaloids in poppy seeds, significantly exceeding the permissible limits defined in Commission Regulation (EU) 2023/91. However, there is relatively limited literature on this topic, highlighting the need for further studies. Future research should focus on other opium alkaloids (papaverine, thebaine, noscapine, and oripavine), which are often overlooked in routine tests for opioids in food products. Additionally, considering that the toxicity of these compounds towards human health is not precisely determined and the potential degradation of these substances during thermal or biological treatments, further knowledge is crucial due to the risks associated with consumer exposure to these compounds through diet. It's important to note that physical or biological methods proposed by researchers for removing these compounds from the surface of poppy seeds may result in derivative products that are sometimes more toxic than the original substances.

The issue of opium alkaloid presence in poppy seeds may be linked to improper production practices or non-compliance with recommendations outlined in Commission Recommendation (EU) 2014/662. Hence, raising awareness among producers about the risks associated with consuming food contaminated with these substances is essential. Routine testing of alkaloid levels in poppy seeds and derived products distributed in the market is also recommended to prevent future breaches of legal limits.

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