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# Opium Alkaloids

*Mahluga Jafarova Demirkapu and Hasan Raci Yananli*

## Abstract

Opium alkaloids, derived from crude *Papaver somniferum* L. plant, are potent analgesic drugs, but their use is limited because of dependence and withdrawal. Opium alkaloids activate the mesocorticolimbic dopaminergic system, which project from the ventral tegmental area to the nucleus accumbens and medial prefrontal cortex, and dopamine is critically important in opioid consumption and sustaining. The reward effect resulting from the activation of the dopaminergic system leads to continued opioid consumption and occurs opioid dependence. After the development of opioid dependence, consumption continues to avoid withdrawal syndrome. Opioid dependence is accompanied with tolerance, which requires the use of high doses to achieve the same effect. When tolerance develops, the chronic consumer continues to use opioid above known toxic doses to produce the same effect, which can result in death regardless of the type of opioid used. Raw *Papaver somniferum* L. has five high-density main opium alkaloids including morphine, noscapine, codeine, thebaine, and papaverine. Some of these alkaloids bind to classical opioid receptors to produce an opioid-like effect, while the other part mediates non-opioid effects. This chapter reviews the opiod history, receptors, mechanism of action, dependence, withdrawal. In addition, general information about five main opium alkaloids, their effects, uses, routes of administration, pharmacokinetics, adverse reactions, contraindications; effects on reproduction, pregnancy, and lactation were compiled.

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

## 1. Introduction

Opium alkaloids are products obtained from the mature capsules of *Papaver somniferum* L. plant in natural way or in laboratory. Although the maintenance of *Papaver somniferum* L. is very easy, obtaining opium alkaloids naturally requires a process. Maturation of capsules occurs in May or June. First, the mature capsules are incised several times to allow the latex to flow. The exposed white latex turns brown with the effect of air. The thickened and solidified latex is collected the next day, dried under suitable conditions and made ready for use [1]. The natural way of extracting opium alkaloids for medical purposes is dried capsules [2]. The main opium alkaloids found in raw *Papaver somniferum* L. and some information are summarized in **Table 1**.

### 1.1 History

*Papaver somniferum* L. is one of the oldest medicinal plants. The first information about the production of opium alkaloids is found on Sumerian clay tablets inscribed

	Density (avg%) [3]	Molecular formula	Molecular weight (g/mol)
Morphine	11.4	C <sub>17</sub> H <sub>19</sub> NO <sub>3</sub>	285.34
Noscapine	8.1	C <sub>22</sub> H <sub>23</sub> NO <sub>7</sub>	413.4
Codeine	3.5	C <sub>18</sub> H <sub>21</sub> NO <sub>3</sub>	299.4
Thebaine	3.2	C <sub>19</sub> H <sub>21</sub> NO <sub>3</sub>	311.4
Papaverine	3.1	C <sub>20</sub> H <sub>21</sub> NO <sub>4</sub>	339.4

**Table 1.**  
*The main opium alkaloids found in crude Papaver somniferum L. and some information.*

in Cuneiform script in about 3000 BC. The Sumerians, whose culture developed between the Tigris and Euphrates Rivers in the south of Iraq between 4000 and 3000 BC, called the opium alkaloids “Gil” (“happiness”) [4].

Opium alkaloids were first isolated in 1803 by Parisian Derosne, and named ‘opium salt’. Friedrich Wilhem Adam Serturner described the ‘opium salt’ in detail in 1817 and named “morphine”, inspired by the Morpheus (Greek god of dreams). Karl Friedrich Wilhelm Meissner first used the word ‘alkaloid’ in 1818, which we still use. Opioids were widely used for the first time in the Franco-Prussian War and the American Civil War for medical purposes. Tincture and pills were preferred for the purpose of analgesia in wounded soldiers. Repeated use caused opioid dependence on some soldiers, and this event was first described as “soldiers’ disease” [5].

1.2 Opioid receptors

Although morphine and other opioid alkaloids are exogenous substances, they show agonistic effect by binding to the receptors of endogenous opioids. Opioid receptors were first described by Beckett and Casy in 1954 [6]. In 1965, Portoghesi and colleagues shared their views on the existence of multiple opioid receptor types [7]. High-affinity and stereospecific binding sites for opioid alkaloids were also found in brain in 1973 [8]. The presence of specific opioid receptors led to the discovery of endogenous ligands. They are enkephalins [9], β-endorphin [10], and dynorphins [11]. The classic opioid receptors, were discovered in 1976–1977 and named after the prototypic drugs or tissue used in these studies: μ (mu, for morphine), δ (delta, for deferens), and κ (kappa, for ketocyclazocine) [12, 13]. These receptors show seven transmembrane domain structures specific to G protein-coupled receptors, are induced by morphine and antagonized by naloxone, and had similar analgesic effect. In 1995, the fourth opioid receptor, which is similar in structure with and closely related to classic opioid receptors, was also discovered [14, 15]. Fourth opioid receptor initially identified as ORL1 or LY132, it was later updated to N/OFQ by taking the name of its endogenous ligands (nociceptin/orphanin FQ) [16]. Although the effects of N/OFQ receptor are not fully known, they do not have a similar effect on pain as classical opioid receptors, and their sensitivity to naloxone is very low. σ (sigma), ε (epsilon), and ζ (zeta) receptors and λ (lambda) site are included in other opioid receptors [17]. The σ receptor, discovered in 1976, is not coupled to G protein, and its effects are not antagonized by naloxone [12, 18, 19]. The ε receptor is sensitive to β-endorphin [20]. The λ site regulates cell growth and is not antagonized by naloxone [21, 22]. Further information on opioid receptors is summarized in **Table 2**.

According to the studies, μ receptor was also related with addiction [38], modulation of dopaminergic system [39], learning and memory [40]. The δ receptors along with μ receptors contribute to emotional sensitivity [41].

Opioid receptors		μ receptor	δ receptor	κ receptor	N/OFQ receptor
Other names		OP3, MOP, MOPr, Mu 1	OP1, DOP, DOR, DOPr, DOR-1	OP2, KOP, KOPr, KOR-1	OP4, KOR-3, NOCIR, kappa3-related, MOR-C, nociceptin receptor ORL, XOR1, NOP-r, nociceptin/orphanin FQ, NOPr
Regions with high distribution	CNS	Thalamus Caudate putamen Neocortex Nucleus accumbens (NAc) Amygdala Interpeduncular complex Inferior and superior colliculi [23]	Olfactory bulb Neocortex Caudate putamen NAc Amygdala [23]	Cerebral cortex NAc Clausstrum Hypothalamus [23, 24]	Cerebral cortex Anterior olfactory nucleus Lateral septum Ventral forebrain Hippocampus Hypothalamus Amygdala Substantia nigra Ventral tegmental area (VTA) Locus coeruleus Brain stem nuclei [25]
	Spinal cord	Superficial layers dorsal horn of spinal cord [26]			Dorsal horn [25]
	Non-CNS	Skin [27] Immune cells [29] Pregnant uterus [31] Gastrointestinal (GI) tract [32] Cochleae [34]	Skin [28] Immune cells [30] Pregnant uterus [31] GI tract [33] Cochleae [34]	Skin[28] Immune cells [30] Pregnant uterus [31] GI tract [33] Cochleae [34]	
	Types of G-protein	Primary: Gi/Go Secondary: Gq/G11	Gi/Go	Primary: Gi/Go Secondary: G12/G13	Primary: Gi/Go
Endogenous ligands		β-endorphin Enkephalins Endomorphin-1 and -2	β-endorphin Enkephalins	Dynorphin A Dynorphin B α-neoendorphin	Nociceptin Orphanin FQ
Agonists [from main opium alkaloids]		Morphine Codeine	Morphine	Morphine	
Antagonists		Naloxone Naltrexone	Naloxone Naltrexone	Naloxone Naltrexone	[Nphe <sup>1</sup> ]N/OFQ-(1-13)-NH <sub>2</sub> UFP-101
Effects		Analgesia Respiratory functions Cardiovascular functions GI motility Neuroendocrine functions Immune system functions Feeding Mood Thermoregulation [35]	Analgesia [36] Cardiovascular functions GI motility Mood Behaviour [15]	Analgesia Neuroendocrine functions Immune system functions Diuresis Feeding [35]	Nociception Motor and aggressive behaviours Reinforcement and reward Stress response Autonomic system functions Immune system functions [37]

**Table 2.**  
*Opioid receptors and their properties.*

### 1.3 Mechanism of action

$\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors are distributed in peripheral tissue as well as CNS. Stimulation of these receptors in the CNS results in analgesia, drowsiness, euphoria, a sense of detachment, respiratory depression, nausea and vomiting, depressed cough reflex, and hypothermia. When these receptors are stimulated in peripheral tissues, miosis, orthostatic hypotension, constipation, urinary retention etc. emerges.

After stimulation of these  $G_i/o$ -coupled opioid receptors, the adenylate cyclase enzyme is suppressed and the level of cyclic AMP decreases. In addition, the voltage-gated calcium channels in the axon ends or neuron soma are closed and intracellular calcium levels are reduced, potassium channels are opened and leading to an increase in potassium conductance. As a result, inhibition and hyperpolarization of neurons occurs when opioid receptors are stimulated [42, 43].

Analgesic or antinociceptive effects, which are indicated for use of opioids, develop at the level of the brain and spinal cord. At the brain level, attenuation of impulse spread is weakened and the perception of pain is inhibited, and at the spinal cord level, the transmission of pain impulses is suppressed [44].

### 1.4 Opioid dependence

Opioid dependence or addiction is a chronic, recurrent disease that changes neurotransmitter systems in the CNS and affects movement [45, 46]. Opioid dependence develops in both psychic and physical dependence. Physical opioid dependence occurs both when used for treatment and as a result of abuse. Opioid abuse is a relapsing disease with high morbidity and mortality, which is used at higher doses to produce the same effect due to tolerance. The higher the exposure time to opioids, the higher the degree of dependence and tolerance. After physical dependence develops, opioid consumption is maintained to prevent withdrawal symptoms. So the treatment is long and difficult. For this purpose, opioid agonists such as methadone, buprenorphine, an opioid antagonist naltrexone or abstinence-based treatment may be preferred. This disease, referred to as 'opioid abuse and opioid dependence' in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSMIV-TR), has been changed to 'opioid use disorder' in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [47].

The estimated annual prevalence of opioids in 2010 was 0.6–0.8% of the population aged 15–64 ( $26 \times 10^6$  to  $36 \times 10^6$ ). The estimated annual prevalence of opioid use is between 0.3 and 0.5% of the adult population ( $13 \times 10^6$  to  $21 \times 10^6$  past-year users) [48].

The mesocorticolimbic dopaminergic system, which project from the VTA to the NAc and medial prefrontal cortex (mPFC) are critically important in opioid dependence [49]. Opioids act on VTA and directly or indirectly cause an increase in dopamine release in NAc region [50]. In the pathogenesis of opioid dependence, the presence of a complex mechanism including the dopaminergic system, noradrenergic, serotonergic, etc. systems should be considered [51].

### 1.5 Opioid withdrawal

Withdrawal is a condition that occurs when the use of an exogenous substance that is used for a long time and develops physical dependence is interrupted. In opioid dependence, the mesocorticolimbic dopaminergic system activates and induces dopamine release in the NAc region. The adaptive increase in dopaminergic



activity in CNS in opioid dependence is suppressed during withdrawal and withdrawal symptoms appear [52]. In addition to dopamine, different neurotransmitters and neuromodulators, such as noradrenaline, GABA, vasopressin, substance P, neuropeptide Y, and nitric oxide, are thought to play a role in the development of opioid withdrawal [53–55]. In opioid withdrawal syndrome, symptoms such as pain, insomnia, yawning, tremor, lacrimation, rhinorrhea, sweating, dehydration, goosebumps, mydriasis, restlessness, anorexia, nausea, vomiting, diarrhea, weight loss, hyperglycemia, hypotension, decrease in respiratory rate, hyperthermia and abdominal muscle cramps are seen [45].

## 2. The main opium alkaloids in raw *Papaver somniferum* L. and their pharmacological properties

### 2.1 Morphine

International Union of Pure and Applied Chemistry (IUPAC) name:  
(4R,4aR,7S,7aR,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol.

ATC Code	N-Nervous system	N02- Analgesics	N02A- Opioids	N02AA-Natural opium alkaloids	N02AA01- Morphine
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Morphine is one of the major opium alkaloids isolated from plant *Papaver somniferum* L., produced synthetically and metabolized by codeine and heroin in the body. It binds to  $\mu$ ,  $\delta$ , and  $\kappa$  receptors, which are widely distributed in CNS and peripheral tissue, and produce effects such as analgesia, anxiolysis, euphoria, sedation, respiratory depression, and contraction of smooth muscles of GI tract. Morphine is used in the management of severe pain, treatment of acute pulmonary edema and anesthetic procedures [56]. It can be administered orally, rectally, intramuscularly, intravenously, subcutaneously, epidurally, and intrathecally.

Absorption of morphine is variable, an almost complete absorption mainly done in the upper intestine as well as in the rectal mucosa. Morphine presents significant first-pass metabolism and oral bioavailability within 17–33% [57]. Morphine distributes to brain, skeletal muscle, liver, kidneys, lungs, intestinal tract, and spleen [58]. Hepatic metabolism occurs via glucuronic acid conjugation primarily to morphine-6-glucuronide (M6G, 10–15%) and morphine-3-glucuronide (M3G, 45–55%). Other metabolites include morphine-3,6-diglucuronide, morphine-3-etheral sulphate, normorphine, normorphine-6-glucuronide, normorphine-3-glucuronide and codeine. M6G and normorphine show active analgesic effect by binding to opioid receptors, but M6G, which is formed more than normorphine, can contribute to analgesic effect of morphine. M3G does not contribute to the analgesic effect of morphine, because it has low affinity to opioid receptors [59]. Half-life elimination is variable according to age group: in neonates 4.5–13.3 h, in children 1–2 h, and in adults 2–4 h. Excretion occurs with urine (2–12%) and feces (7–10%).

Morphine leads to death in amounts of 0.15–0.2 g (sc) or 0.3–0.4 g (oral) in adults. Babies and young children are much more susceptible, and death has been observed at doses of 30 mg [60]. Morphine blood concentration within 10–100  $\mu\text{g/dL}$  is toxically; if it is above 400  $\mu\text{g/dL}$  is lethally [61].

Common adverse reactions are drowsiness, headache, constipation, nausea, vomiting, urinary retention. Although less common adverse reactions, such as depression, insomnia, paresthesia, dizziness, anxiety, abnormal dreams, confusion, seizure, myoclonus, agitation, amnesia, euphoria, pain, dyspnea, hypoventilation,

respiratory depression, tremor, fever, flu-like symptoms, rhinitis, edema, hypotension, syncope, palpitations, skin rash, amblyopia, blurred vision, conjunctivitis, diplopia, miosis, nystagmus, amenorrhea, impotence, gynecomastia, urinary hesitancy, diaphoresis, anorexia, biliary colic, dyspepsia, gastroesophageal reflux disease, hiccups, xerostomia, anemia, thrombocytopenia can be seen.

Contraindications are hypersensitivity to morphine, significant respiratory depression, acute or severe bronchial asthma in the absence of resuscitative equipment, GI obstruction.

*Effects on reproduction:* Prolonged morphine use can cause secondary hypogonadism, which can lead to infertility in both sexes [62].

*Effects on pregnancy:* It is known that, morphine crosses the placenta. Morphine exposure was associated with conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifid, and gastroschisis within a 4-month period, 1 month before and 3 months after conception [63]. In addition, the use of it in the first trimester may reduce fetal heart rate from non-teratogenic effects [64]. Use of morphine late in pregnancy may result in decreased fetal breathing movements or withdrawal signs in the newborn [65, 66]. Withdrawal signs are hypothermia, hyperthermia, diarrhea, vomiting, anorexia, weight gain, high-pitched crying, hyperactivity, increased muscle tone, increased wakefulness, abnormal sleep pattern, irritability, sneezing, seizure, tremor, yawning and etc. [67, 68].

*Effects on lactation:* Both morphine and an active metabolite, M6G, can be detected in breast milk [69]. According to previous study, a milk:plasma ratio of morphine was 2.85, and the estimated maximum concentration in milk was 500 ng/mL [70]. Respiratory depression or drowsiness were not common in infants of breastfeeding mothers receiving morphine [71]. Although not preferred in lactation, it should be used as soon as possible and at the lowest dose if necessary [72].

2.2 Noscapine

IUPAC name: (3S)-6,7-dimethoxy-3-[(5R)-4-methoxy-6-methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-5-yl]-3H-2-benzofuran-1-one.

ATC Code	R-Respiratory system	R05-Cough and cold preparations	R05D-Cough suppressants, excl. combinations with expectorants	R05DA-Opium alkaloids and derivatives	R05DA07-Noscapine
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Noscapine, also known as narcotine, is the second opioid alkaloid according to its density in raw *Papaver somniferum L.* plant, was first isolated by Robiquet in 1817 [73]. Noscapine has no morphine-like effect, no affect on morphine withdrawal and has mild analgesic effect [74]. It is used to suppress cough frequency and intensity in bronchial asthma and pulmonary emphysema as it has central antitussive activity such as codeine [74, 75]. It is thought that noscapine exerts its antitussive effect through  $\sigma$  receptor which is one of the other opioid receptors. Repeated exposure to noscapine does not lead to dependence and tolerance to its antitussive effect does not develop. The potential for antineoplastic treatment is being investigated because of its antimetabolic effect [76]. In the animal study, noscapine increased histamine release, leading to bronchoconstriction and hypotension, even convulsions [77]. There are also studies showing that teratogen [78]. Noscapine is used orally in the form of a combined preparation to reduce these effects.

Noscapine in terms of antitussive potency, onset, and duration of action is similar to codeine, one of the main opium alkaloids [74]. Noscapine has a relatively low bioavailability due to a first-pass metabolism [79]. Noscapine is inactivated by

converting into meconin and o-demethylated metabolites. Meconin is major urinary metabolite of noscapine [80].

Adverse reactions are not expected when used in therapeutic doses [74]. When taken in high doses, drowsiness, headache, nausea, vasomotor rhinitis, conjunctivitis may be seen [81].

*Effects on reproduction and pregnancy* is unknown.

*Effects on lactation:* It is thought to have no negative effects on infant [82].

2.3 Codeine

IUPAC Name: (4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol

ATC Code	R-Respiratory system	R05-Cough and cold preparations	R05D-Cough suppressants, excl. combinations with expectorants	R05DA-Opium alkaloids and derivatives	R05DA04-Codeine
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Codeine, a 3-methylether derivative of morphine, is the third opioid alkaloid according to its density in the raw *Papaver somniferum* L. plant, was first isolated by Robiquet in 1833. Codeine and its metabolite, morphine, act by stimulating opioid receptors. The main effects are analgesia (lighter than morphine), central antitussive and antidiarrheal effects [83]. It can also do sedation, drowsiness, and respiratory depression. Codeine is used in the management of mild to moderate pain, in the treatment of cough, persistent diarrhea and restless leg syndrome. Codeine is taken orally and intramuscularly.

Absorption is rapidly in oral use and bioavailability is higher due to less first-pass metabolism (about 53%). Codeine is distributed to a variety of tissues, with priority being to the liver, spleen and kidney [84]. Codeine-6-glucuronide, morphine, and norcodeine is formed as a result of hepatic metabolism. Morphine is then metabolized to M3G and M6G, and contributes to analgesic effects of codeine. The half-life elimination is about 3 h and excretion is mostly done through urine and with less feces.

In adults 7–14 mg/kg, in children more than 5 mg/kg intake leads to death [85]. Codeine blood concentration within 20–50 µg/dL is toxically, if it is above 60 µg/dL is lethally [86].

Abnormal dreams, insomnia, depression, paresthesia, agitation, anxiety, ataxia, dizziness, disorientation, sedation, euphoria, fatigue, hallucination, headache, bradycardia, tachycardia, circulatory depression, flushing, pruritus, skin rash, urticaria, bronchospasm, dyspnea, respiratory depression, abdominal cramps, anorexia, constipation, diarrhea, nausea, urinary hesitancy, urinary retention, blurred vision, diplopia, miosis, nystagmus, laryngospasm, muscle rigidity, tremor, hypogonadism, etc. may occur due to codeine use.

Contraindications are hypersensitivity to codeine, pediatric patients <12 years of age, postoperative management in pediatric patients <18 years of age who have undergone tonsillectomy and/or adenoidectomy, significant respiratory depression, acute or severe bronchial asthma in the absence of resuscitative equipment, GI obstruction.

*Effects on reproduction:* Prolonged codeine use can cause secondary hypogonadism, which can lead to infertility in both sexes [62].

*Effects on pregnancy:* It is known that, codeine crosses the placenta. The use in the first trimester can lead to respiratory tract malformation, pyloric stenosis, inguinal hernia, neural tube defects, cardiac and circulatory system defects, and cleft lip and palate [63, 87]. The use of codeine late in pregnancy may result in neonatal



withdrawal syndrome, characterized by tremor, jitteriness, diarrhea, and poor feeding [88].

*Effects on lactation:* Both codeine and an active metabolite, morphine, can be detected in breast milk [89]. A milk: plasma ratio of codeine is unknown. Respiratory depression, sedation and withdrawal signs can be seen in infants of breastfeeding mothers receiving codeine [90].

2.4 Thebaine

IUPAC Name: (4R,7aR,12bS)-7,9-dimethoxy-3-methyl-2,4,7a,13-tetrahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline.

Thebaine, also known as paramorphine, which is not used for medicinal purposes and is used for the production of other opioids, is the fourth opioid alkaloid according to its density in the raw *Papaver somniferum* L. plant. Thebaine exposure can be addictive as in the use of morphine, as well as strychnine-like convulsions [91].

2.5 Papaverine

IUPAC name: 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline

ATC Code	A-Alimentary tract and metabolism	A03-Drugs for functional gastrointestinal disorders	A03A-Drugs for functional gastrointestinal disorders	A03AD-Papaverine and derivatives	A03AD01-Papaverine
	G-Genito urinary system and sex hormones	G04-Urologicals	G04B-Urologicals	G04BE-Drugs used in erectile dysfunction	G04BE02-Papaverine

Papaverine, which has no opioid-like effect, is the fifth opioid alkaloid based on its density in the raw *Papaver somniferum* L. plant, first isolated from opium by Merck in 1848. Papaverine affects the heart muscle and vascular smooth muscle by blocking non-selective phosphodiesterase and calcium channels [92]. Papaverine suppresses conduction and prolongs the refractory period in the heart. Vasodilation occurs with direct effect on vascular smooth muscles including coronary and pulmonary arteries. Papaverine-mediated relaxation in smooth muscles is independent of muscle innervation and therefore does not cause paralysis in the muscles. Papaverine-mediated these effects are more pronounced especially in ischemia with arteriospasm [93]. Papaverine is used in the treatment of myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease, cerebral angiospastic states. It can also be used in hypertension, urinary incontinence, prostate hyperplasia and erectile dysfunction [94]. Papaverine also has antiviral activity, which is particularly pronounced against respiratory syncytial virus, cytomegalovirus and HIV [95]. Papaverine is taken orally, intramuscularly, intravenously, and intra-arterially.

Absorption is nearly total in oral use. Oral bioavailability is higher due to less first-pass metabolism (about 54%). Papaverine is distributed to a variety of tissues, with priority being to the adipose tissue and liver. 6-Desmethylpapaverine (6-DMP, major metabolite) and 4',6-didesmethylpapaverine (4,6-DDMP) is formed as a result of hepatic metabolism [96]. Half-life elimination is 0.5–2 h. The excretion of papaverine is through primarily urine [97]. No information on toxic blood concentrations is available. The oral median lethal dose in rats is 360 mg/kg, unknown in humans [98].

Adverse reactions are flushing, hypertension, tachycardia, headache, malaise, sedation, abdominal distress, anorexia, constipation, etc.

Use in the complete AV block is contraindicated.

*Effects on reproduction and lactation* is unknown.

*Effects on pregnancy*: It is not considered to have a adverse effect on infants.

### 3. Conclusions

Although information about opium alkaloids was about 3000 BC, it was first isolated in the 1800s. Opioid-like effects occur after opioid alkaloids bind to conventional opioid receptors, such as  $\mu$ ,  $\delta$ , and  $\kappa$ . In particular, as a result of the agonistic effect on  $\mu$  receptors, strong analgesia, physical dependence, tolerance and increased dopaminergic activity develop in the mesocorticolimbic system responsible for dependence. Increased dopaminergic activity in the mesocorticolimbic system, is a sign of developing physical dependence, decreases in the absence of opium alkaloids, leading to withdrawal syndrome. Hypogonadism in opium alkaloids users supports the idea that it has a suppressive effect on reproduction. In addition to the risk of teratogenicity, use in both pregnancy and lactation may lead to the development of abstinence syndrome in infants.

### Conflict of interest

The authors declare no conflict of interest.

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