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Original Article

Investigation of the Inhibitory Effect of Naringin on the Development of Morphine Physical Dependency in Male Rats

Atena Alifarsangi[1], Saeed Esmaeili-Mahani[1,2*], Ehsan Salarkia[3], Elham Alizadeh[1], Mehdi Abbasnejad[2]

[1]Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Biology, Faculty of Sciences, Shahid Bahonar University of Kerman, Kerman, Iran
[3]Leishmaniasis Research Center, Kerman University of Medical Sciences, Kerman, Iran

*__Corresponding Author:__ Saeed Esmaeili-Mahani, Email: semahani@uk.ac.ir

Abstract

Background: Morphine dependence is a significant concern because of its potential for inducing addiction and adverse withdrawal symptoms. Naringin, a flavonoid compound found in citrus fruits, has shown promise in various pharmacological activities, including analgesic and anti-inflammatory effects. However, its potential role in inhibiting or reducing morphine dependence has not been extensively investigated yet. This study aimed to determine whether naringin can inhibit or reduce physical morphine dependence in rats.

Methods: Morphine dependence was induced in rats through chronic injection of the drug for 7 days. Also, different doses of naringin (10, 25, and 50 mg/kg) were administered 15 minutes prior to morphine injection in three experimental groups. The effect of naringin pretreatment on drug withdrawal-associated symptoms, including body weight, jumping, abdominal contraction, grooming, ptosis, diarrhea, and teeth chattering, was evaluated.

Finding: The animals experiencing morphine dependence exhibited significant body weight loss. However, administration of naringin before morphine injection prevented this loss by 50%. Also, drug withdrawal symptoms such as jumping, abdominal contraction, grooming, diarrhea, and teeth chattering were significantly increased in the rats. Interestingly, the prescription of naringin significantly reduced these symptoms. Ptosis was observed in all rats receiving morphine, while naringin did not significantly affect this symptom. Furthermore, the inhibitory effect of naringin on morphine physical dependence was found to be dose-dependent.

Conclusion: Naringin pretreatment demonstrated potential in inhibiting or reducing physical morphine dependence in rats. These findings suggest that naringin may have therapeutic potential in managing morphine dependence and associated withdrawal symptoms.

Keywords: Morphine dependence, Naringin, Drug withdrawal

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Introduction

Morphine, a powerful pain reliever belonging to the opioid family, is commonly prescribed to treat intense pain. However, non-medical use, extended use, misuse, or use without proper medical supervision can cause opioid dependence, a state characterized by the emergence of withdrawal symptoms upon cessation of drug administration.[1] The development of morphine dependence poses significant challenges in clinical settings, as it can lead to addiction, tolerance, and withdrawal symptoms, ultimately impacting patient outcomes and quality of life. Studies have shown that individuals with opioid dependence, including morphine, often experience impaired physical and mental health, reduced social functioning, and diminished overall well-being.[2,3] There are treatment options available for opioid dependence that can reduce the risk of overdose. Unfortunately, only 50% of countries offer access to the treatments, and globally, less than 10% of people who require such treatment receive it.[4] Thus, it is increasingly important to investigate and discover substances that can impede or lessen the formation of physical dependence on morphine.

Understanding the mechanisms underlying the development of morphine dependence is crucial for the development of effective therapeutic interventions. Several studies have investigated the neurobiological adaptations that happen in the brain due to long-term exposure to morphine. These adaptations include alterations

in synaptic plasticity, neurotransmitter systems, and receptor expression.[5,6] For instance, the activation of the mu-opioid receptors (MORs) by morphine leads to downstream signaling events that contribute to the development of dependence.[7] Consequently, investigating compounds that can modulate MOR signaling or target other neurobiological pathways associated with morphine dependence may offer promising strategies for preventing or attenuating the development of physical dependence.

Naringin is a natural flavonoid compound founds in various citrus fruits, particularly grapefruits. The chemical structure of this compound includes a flavonoid nucleus with multiple hydroxyl groups.[8] Recently, naringin has been extensively received *a lot of attention for* its potential biological impact and health benefits. It shows anti-inflammatory, antioxidant, antimicrobial and anticancer activities.[9-12] Furthermore, it has demonstrated potential in cardiovascular health by reducing cholesterol levels, improving blood lipid profiles, and exerting vasodilatory effects.[13] With its distinctive chemical structure and well-documented biological properties, naringin holds promise as a potential agent for reducing or inhibiting the development of morphine physical dependency. It is expected that naringin can interact with opioid receptors and due to its anti-inflammatory and antioxidant properties, potentially contribute to modulating the processes involved in physical dependency.

This study's objective was to explore the inhibitory/reducing effects of naringin on the induction of morphine physical dependency in a rat model. Toward this end, the rats that revised only morphine for 7 days a row were compared with those that before morphine received naringin. Effect of naringin pretreatment on drug withdrawal symptoms, including body weight, jumping, abdominal contraction, grooming, ptosis, diarrhea, and teeth chattering, was evaluated.

Methods

Animals and treatment groups

In order to conduct the study, 42 adults male Wistar rats weighing between 200-250 g were procured from the Laboratory Animal Maintenance and Breeding Center of Kerman University of Medical Sciences. The rats were housed under controlled conditions, with a temperature of 23 ± 1 °C and a 12:12 hours light/dark cycle, and were provided with free access to food and water. Prior to testing, the rats were given a week to get accustomed to their new surroundings.

During this study, all experiments were performed following the Neuroscience Research Center of Kerman University of Medical Sciences and Neuroscience Ethics Committee guidelines (Ethics Code: EC/KNRC/92-8).

The animals were divided into the following groups (n = 7);

- Control: the intact rats
- Morphine: rats that daily received increasing doses of morphine (to induce dependence)
- Morphine + normal saline (vehicle): rats that daily received increasing doses of morphine (to induce dependence) following treatment with normal saline
- Morphine + naringin 10: rats that daily received increasing doses of morphine following treatment with 10 mg/kg of naringin
- Morphine + naringin 25: rats that daily received increasing doses of morphine following treatment with 25 mg/kg of naringin
- Morphine + naringin 50: rats that daily received increasing doses of morphine following treatment with 50 mg/kg of naringin

Induction of morphine dependence

The induction of morphine dependence in animals was performed by repeated administration of escalating doses of morphine over several days. Briefly, for a week, morphine was administered twice a day with a 10-hour break between doses. The doses were gradually increased starting with 2.5 mg/kg on the first and second day, followed by 5 mg/kg on the third day, 10 mg/kg on the fourth day, 20 mg/kg on the fifth day, and 40 mg/kg on the sixth day. On the seventh (final day) of injection, a dose of 50 mg/kg morphine was administered.

Naloxone tests for morphine dependence assay

The naloxone test was used to measure the animals' dependence on the morphine. In this method, naloxone is used to block morphine receptors acutely.[14] Toward this end, 5 hours after the last morphine injection, on the seventh day, 3 mg/kg of naloxone was intraperitoneally injected into the subjects. Then, each rat was accommodated in a glass chamber, and the opioid-like withdrawal symptoms, such as ptosis, abdominal constrictions, jumping, teeth chattering, diarrhea, and weight loss, were monitored.

In the end, the mean of features, including weight loss, the number of abdominal constrictions, jumping, and grooming was expressed numerically. Also, the presence or absence of diarrhea, teeth grinding, and ptosis in the subjected animals were estimated in relation to the total number of animals in the group.

Naringin treatment

To evaluate the naringin treatments, the animals were divided into three groups subjected to 10, 25, and 50 mg/kg of this compound. To prepare naringin for injection, the intended amount of the drug was weighted and solved in normal saline. Each rat in these groups received the intended concentration of naringin via intraperitoneal injection, 15 minutes before receiving morphine.

Statistical analysis

In order to statistically analyze these data, the SPSS software version 19 was used. Normality of the data was confirmed by the Kolmogorov–Smirnov or the Shapiro–Wilk test. The results were analyzed for statistical significance by pair t-test and one-way ANOVA test by using Tukey's post hoc multi-comparison. In all calculations, P value < .05 was taken as significant. The data were presented as mean ± SEM.

Results

Effects of morphine dependence and naringin treatment on body weight

In the present study, given morphine over a long period of time, it was observed that they experienced significant weight loss upon withdrawal of the drug, as compared to a control group. The weight loss in this group was eight times more than the control group. However, when rats were given naringin 15 minutes before morphine injection, their weight loss was significantly reduced. Prescription of 50 mg/kg of naringin could prevent weight loss by 50% (four times lower than nontreated ones). The study also found that the effectiveness of naringin was dose-dependent. The highest dose of naringin (50 mg/kg) resulted in the lowest weight loss, but even doses of 10 and 25 mg/kg were effective in preventing weight loss in the rats (Figure 1).

Effects of morphine dependence and naringin treatment on jumping

According to the results presented in Figure 2, the rats that received morphine 7 days in a row and then had the drug withdrawn displayed a significant increase in the number of jumps observed, with the average number of jumps reaching around 9. On the other hand, the rats that received naringin prior to morphine had a much lower average number of jumps. In fact, administering 10, 25, and 50 mg/kg of naringin reduced the mean number of jumps to 5, 4.5, and 4, respectively.

Effects of morphine dependence and naringin treatment on abdominal contraction

As Figure 3 shows, the rats who received morphine for 7 consecutive days endured a greater number of abdominal contractions when the drug was withdrawn. This symptom was observed in the rats over ten times in an hour. However, rats that were treated with naringin displayed more stability, as receiving doses of 10, 25, and 50 reduced the number of contractions to 8, 5, and 3 times respectively in 60 minutes.

Effects of morphine dependence and naringin treatment on grooming

After drug withdrawal, the group that received only morphine had a mean number of grooming activities 10 times higher than the control group in 60 minutes. At the same time, pretreatment of the rats with different concentrations of naringin before morphine injection could significantly reduce this feature. The mean number of grooming in the animals that received 10, 25, and 50 mg/kg of this compound decreased to 6.5, 5, and 4, respectively (Figure 4).

Effects of morphine dependence and naringin treatment on Ptosis

According to the results, rats who received morphine on a chronic basis developed ptosis during drug withdrawal at every time interval (Table 1). Naringin, unlike to others, had no effect on this symptom in any of the concentrations.

Effects of morphine dependence and naringin treatment on Diarrhea

Diarrhea caused by drug withdrawal was significantly increased in rats chronically treated with only morphine compared to the control group. However, receiving 50 mg/mL of Naringin before morphine injection caused a significant decrease in the number of animals with diarrhea (Table 2). Only 2 out of 7 rats exhibited diarrhea, 30 minutes after induction of drug withdrawal using naloxone.

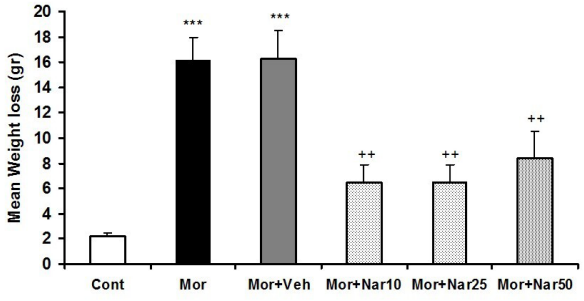

Figure 1. The effect of morphine dependence (Mor) and naringin treatment (Nar 10, 25, and 50 mg/kg) on animals' body weight. Results are shown as mean ± SEM. *** indicates a significant difference compared to the control group (P < 0.001) and ++ shows a significant difference compared to the morphine group or the Mor + Nar group

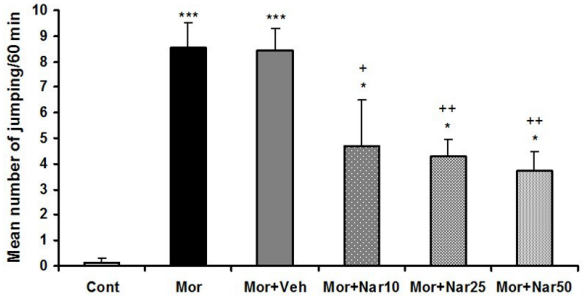

Figure 2. The effect of morphine dependence (Mor) and naringin treatment (Nar 10, 25, and 50 mg/kg) on animals' jumping. Results are shown as mean ± SEM. *** indicates a significant difference compared to the control group (P < 0.001), + (P < 0.05) and ++ (P < 0.01) show a significant difference compared to the morphine group or the Mor + Nar group

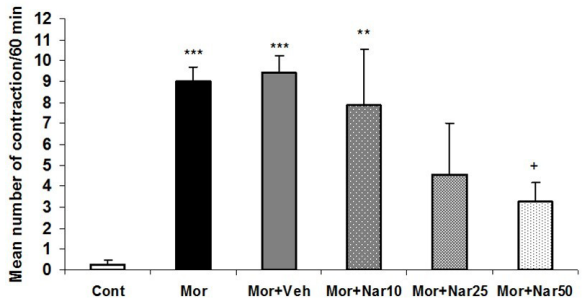

Figure 3. The effect of morphine dependence (Mor) and naringin treatment (Nar 10, 25, and 50 mg/kg) on animals' abdominal contractions. Results are shown as mean ± SEM. ** and *** indicate a significant difference compared to the control group at $P<0.01$ and $P<0.001$, respectively. + ($P<0.05$) shows a significant difference compared to the morphine group or the Mor + Nar group

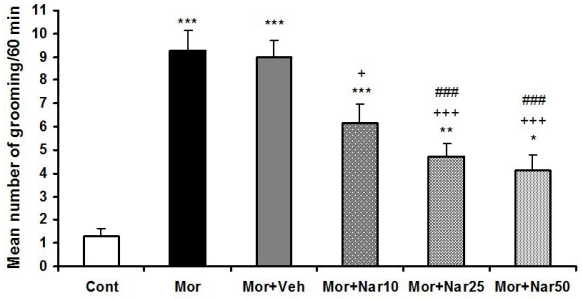

Figure 4. The effect of morphine dependence (Mor) and naringin treatment (Nar 10, 25, and 50 mg/kg) on animals' grooming. Results are shown as mean ± SE. *, **, and *** indicate a significant difference compared to the control group at $P<0.05$, $P<0.01$, and $P<0.001$, respectively. + and +++ show a significant difference compared to the morphine group at $P<0.05$ and $P<0.001$. ### shows significant differences at $P<0.001$ compared to the Mor + Nar group

Table 1. The number of animals with Ptosis in each group of 7

Groups	The number of rats showing symptoms (out of 7 rats)			
	First 15 min	Second 15 min	Third 15 min	Fourth 15 min
Cont	0	0	0	0
Mor	7	7	7	7
Mor + Veh	7	7	7	7
Mor + Nar10	7	7	7	7
Mor + Nar25	7	7	7	7
Mor + Nar50	7	7	7	7

Mor: morphine, Nar: naringin, Veh: vehicle.

Table 2. The number of animals with Diarrhea in each group of 7

Groups	The number of rats showing symptoms (out of 7 rats)			
	First 15min	Second 15 min	Third 15 min	Fourth 15 min
Control	0	0	0	0
Morphine	7	7	7	7
Mor + Veh	7	7	7	7
Mor + Nar10	5	6	7	3*** +
Mor + Nar25	7	7	5	6**
Mor + Nar50	4	5**	2*** ++	2** ++

** and *** indicate a significant difference compared to the control group at $P<0.01$ and $P<0.001$, respectively. + and ++ show a significant difference compared to the morphine group at $P<0.05$ and $P<0.01$. Mor: morphine, Nar: naringin, Veh: vehicle

Effects of morphine dependence and naringin treatment on teeth chattering

The study found that animals given morphine experienced teeth grinding when naloxone was used to induce drug withdrawal. However, the number of animals with this symptom was lower in the groups that also received naringin. While the effects of 10 and 25 mg/mL of naringin were not significant, a dose of 50 mg/kg was able to significantly reduce teeth grinding in the rats (Table 3).

Discussion

Morphine, a potent opioid analgesic, is commonly used for pain management. However, prolonged use can lead to physical and emotional dependency, making it difficult it to discontinue and finally experiencing withdrawal symptoms. The consequences of morphine dependence can be devastating, impacting not only the individual's physical health but also their social and psychological well-being. Therefore, it is crucial to develop effective strategies and interventions to prevent and treat morphine dependence, including exploring potential inhibitors or reducing agents that can mitigate the development and severity of withdrawal symptoms. The present study showed that naringin can help reduce physical morphine dependence in rats, indicating its therapeutic potential in managing morphine dependence and withdrawal symptoms.

Morphine dependence is associated with weight loss. Consistent with this discovery, previous research has highlighted that individuals who develop a dependence on morphine experience physiological alterations affecting their appetite, metabolism, and overall nutritional status. One potential explanation for weight loss in morphine dependence lies in the drug's impact on the central nervous system, particularly the brain's reward and pleasure centers. Morphine can suppress appetite and diminish food intake and subsequent weight loss.[15] In addition, morphine dependence can affect the body's metabolism. Opioids like morphine can alter the function of the gastrointestinal system, leading to issues such as constipation or slowed digestion. These disruptions can impact nutrient absorption and utilization, contributing to weight loss.[16]

We found that prescription of naringin before morphine injection can effectively reduce the animals weight loss. The exact mechanisms of how naringin may reduce weight loss specifically in morphine dependence are not fully understood; however, there are a few possible explanations based on its known properties. Firstly, naringin has been reported to elicit potent antioxidant and anti-inflammatory effects. Chronic morphine use can induce inflammation in various tissues, including

Table 3. The number of animals with teeth chattering in each group of 7

Groups	The number of rats showing symptoms (out of 7 rats)			
	First 15 min	Second 15 min	Third 15 min	Fourth 15 min
Control	0	0	0	0
Morphine	7	7	7	7
Mor+Veh	7	7	7	7
Mor+Nar10	7	7	7	7
Mor+Nar25	7	7	7	5**
Mor+Nar50	7	5**	6	5**

** and *** indicate a significant difference compared to the morphine group at $P<0.01$ and $P<0.001$, respectively. Mor: morphine, Nar: naringin, Veh: vehicle.

the gastrointestinal tract.[17] By reducing inflammation, naringin may help restore normal gastrointestinal function, improving nutrient absorption and potentially mitigating weight loss. Secondly, naringin has been shown to modulate certain signaling pathways involved in appetite regulation, metabolism, and energy balance.[18,19] It may affect the release of certain hormones and neurotransmitters related to appetite and satiety, potentially influencing food intake and body weight.[20,21]

According to the results, rats dependent on morphine exhibited frequent abdominal contractions and diarrhea after receiving naloxone and undergoing drug withdrawal. These symptoms align with what is commonly observed during morphine withdrawal, consistent with findings from previous studies.[22,23] Abdominal contraction, also known as abdominal cramping, often occurs due to changes in the gastrointestinal tract's normal functioning during morphine withdrawal. Also, diarrhea can be a result of the body's attempt to eliminate toxins and restore normal bowel function after discontinuing morphine use.

Conversely, we noticed that rats administered naringin a few minutes before morphine exhibited a more stable condition. The incidence of abdominal contractions and diarrhea in this group of rats was significantly reduced. This activity of naringin can be attributed to its biological activities. It has been demonstrated that naringin with anti-inflammatory property could inhibit pro-inflammatory cytokines release and inhibit the inflammatory enzymes.[24] Given that inflammation is associated with morphine withdrawal symptoms, reducing inflammation by naringin can alleviate symptoms such as abdominal contraction. Also, naringin exhibits antioxidant properties,[25] which can help reduce oxidative stress caused by morphine withdrawal. Oxidative stress can contribute to inflammation and tissue damage,[26] and reducing oxidative stress may help mitigate symptoms such as diarrhea. This argument has been supported by solid evidence.[27,28]

It has been shown that certain flavonoids, including naringin and naringenin, can affect the movement of the digestive system and the time it takes for food to pass through the intestines by reducing the contractility of smooth muscles.[29] Studies have indicated that naringenin can reduce the potential amplitudes of gastro-intestinal (GI) cell excitability, which leads to a decrease the tone, peristalsis, and transit in the GI tract.[30,31] The inhibitory effects of these compounds on muscle contractions can be explained by their regulating effects on GI hormones and neurotransmitters.[32] Studies have shown that ion channels have a crucial role in adjusting the motility of the GI tract.[33] This means that substances that can alter the activities of ion channels may impact the functioning of GI motility. Activation of K^+ channels is generally believed to hinder the generation of action potentials in smooth muscles, thereby enabling the regulation of their tone through graded changes in membrane potential. Multiple potassium channels including ATP-sensitive K^+ channels are involved in the regulation of potassium conductance in smooth muscle cells.[34,35] It has been documented that naringenin can activate the ATP-sensitive K^+ channel.[36] Furthermore, flavonoids naringenin has calcium blocker properties that can modulate bowel motility

Ptosis, also known as drooping eyelids, is a potential symptom that can occur during morphine withdrawal, while not as commonly reported as other withdrawal symptoms, such as abdominal cramping or diarrhea.[37] However, in this study, this symptom was observed in all rats who received morphine. Morphine acts on opioid receptors in the brain and spinal cord, affecting the release and activity of neurotransmitters. When morphine use is discontinued, the sudden absence of the drug can result in imbalances in neurotransmitter levels, which may contribute to the development of ptosis. Noteworthy, in contrast to other symptoms, pretreating the animals with naringin had no significant impact on improving this feature.

Jumping, grooming and teeth chattering were other features increased in the morphine-dependent rats as a result of drug withdrawal. These are among common symptoms observed in similar investigations.[38,39] These can be associated with increased nervous system activity due to the absence of morphine's sedative effects and increased muscle tension or heightened anxiety during withdrawal.[40] Results of this study suggested that prescription of naringin could significantly reduce these features. Up to now, there is limited scientific research specifically linking naringin consumption to the reduction of morphine withdrawal symptoms, such as jumping, grooming, and teeth chattering. However, naringin has been studied for its potential effects on opioid receptors and opioid withdrawal in animal models.[41] Some studies have suggested that naringin may exhibit certain properties that could be beneficial in managing opioid withdrawal symptoms. For example, it has been shown to interact with the opioid receptor system and modulate the release of certain neurotransmitters involved in pain and addiction pathways.[42]

In the discussion of the most appropriate dose of naringin to for preventing the adverse effects of morphine, the results of the study showed that the dose of 50 mg/kg of naringin showed more appropriate effects.

Studies have shown that drug addiction can trigger the mesolimbic dopaminergic rewarding system and finally increase the level of dopamine in nucleus accumbens.[43,44] The administration of morphine is known to activate astrocytes and microglial cells via μ-opioid receptors, which in turn induces a proinflammatory phenotype. Morphine has been found to activate astrocytes in several regions of the brain, including the prefrontal cortex, locus coeruleus, trigeminal and caudate nucleuses, lateral septum, periaqueductal grey matter and ventral tegmental areas.[45]

Conclusion

Considering the anti-inflammatory activity of naringin, it is highly likely that this biocompound by reducing the inflammation induced by morphine can ameliorate the detrimental effects of morphine dependency.

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Authors' Contribution

Conceptualization: Atene Alifarsangi, Elham Alizadeh, Mehdi Abbasnejad, Saeed Esmaeili-Mahani.
Data curation: Atene Alifarsangi Elham Alizadeh.
Data analysis: Atene Alifarsangi Elham Alizadeh, Saeed Esmaeili-Mahani.
Methodology: Alizadeh, Mehdi Abbasnejad, Saeed Esmaeili-Mahani.
Supervision: Saeed Esmaeili-Mahani.
Writing–original draft: Atene Alifarsangi Elham Alizadeh, Ehsan Salarkia.
Writing–review & editing: Atene Alifarsangi Elham Alizadeh, Ehsan Salarkia, Saeed Esmaeili Mahani.

Competing Interests

There was no conflict of interest.

Ethical Approval

The Animal Experimentation Ethic Committee of Kerman Neuroscience Research Center approved all experiments (Ethics Code: EC/KNRC/92-8).

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