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Original Article

Exploring the antinociceptive potential of homoeriodictyol in nociception models

[Exploración del potencial antinociceptivo del homoeriodictyol en modelos de nocicepción]

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Abstract

Context: Homoeriodictyol is a flavonoid with known antioxidant, anti-inflammatory, and anti-tumor properties found in various plants. However, its potential analgesic effects have not been explored.

Aims: To investigate the pain-relieving properties of homoeriodictyol using different mouse models of nociception.

Methods: Various doses of homoeriodictyol (50, 100, 150, and 200 µg/kg) were administered to mice and evaluated using the acetic acid-induced writhing test, the hot plate test, and the formalin-induced paw licking assay. These effects were compared with those of mice treated with acetylsalicylic acid or morphine, both with and without naloxone, an opioid receptor antagonist. Additionally, capsaicin- and glutamate-induced paw-licking tests were conducted to assess the involvement of the vanilloid and glutamatergic systems, respectively.

Results: Homoeriodictyol demonstrated a significant and dose-dependent reduction in nociceptive behavior in the acetic acid-induced writhing test, achieving a 52.4% inhibition at a dose of 200 µg/kg. It also substantially increased the latency period in response to the hot plate test (65.8% at 200 µg/kg) and significantly suppressed both the neurogenic and inflammatory phases in the formalin-induced paw-licking test. Notably, the effects of homoeriodictyol in the hot plate test and formalin-induced paw-licking test were significantly reversed by naloxone. Furthermore, homoeriodictyol effectively reduced neurogenic nociception induced by intraplantar injections of glutamate and capsaicin (57.8% and 76.9%, respectively, at a dose of 200 µg/kg).

Conclusions: This study concludes that homoeriodictyol exhibits antinociceptive activity in mice, acting through both central and peripheral pathways.

Keywords: glutamate; homoeriodictyol; naloxone; nociception; vanilloid.

Resumen

Contexto: El homoeriodictiol es un flavonoide con conocidas propiedades antioxidantes, antiinflamatorias y antitumorales que se encuentra en diversas plantas. Sin embargo, no se han explorado sus posibles efectos analgésicos.

Objetivos: Investigar las propiedades analgésicas del homoeriodictyol utilizando diferentes modelos de nocicepción en ratones.

Métodos: Se administraron varias dosis de homoeriodictyol (50, 100, 150 y 200 µg/kg) a ratones y se evaluaron mediante el ensayo de retorcimiento inducido por ácido acético, el ensayo de la placa caliente y el ensayo de lamido de la pata inducido por formalina. Estos efectos se compararon con los de ratones tratados con ácido acetilsalicílico o morfina, con y sin naloxona, un antagonista de los receptores opioides. Además, se realizaron pruebas de lamido de la pata inducidas por capsaicina y glutamato para evaluar la implicación de los sistemas vanilloide y glutamatérgico, respectivamente.

Resultados: El homoeriodictiol demostró una reducción significativa y dependiente de la dosis del comportamiento nociceptivo en la prueba de retorcimiento inducido por ácido acético, alcanzando una inhibición del 52,4% a una dosis de 200 µg/kg. También aumentó sustancialmente el período de latencia en respuesta a la prueba de la placa caliente (65,8% a 200 µg/kg) y suprimió significativamente tanto la fase neurogénica como la inflamatoria en la prueba de lamido de la pata inducida por formalina. En particular, los efectos del homoeriodictyol en la prueba de la placa caliente y en la prueba de lamido de la pata inducido por formalina se invirtieron significativamente con la naloxona. Además, el homoeriodictyol redujo eficazmente la nocicepción neurogénica inducida por inyecciones intraplantar de glutamato y capsaicina (57,8% y 76,9%, respectivamente, a una dosis de 200 µg/kg).

Conclusiones: Este estudio concluye que el homoeriodictyol exhibe actividad antinociceptiva en ratones, actuando tanto a través de vías centrales como periféricas.

Palabras Clave: homoeriodictyol; glutamato; naloxona; nocicepción; vanilloide.

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INTRODUCTION

Pain, a multifaceted experience stemming from tissue harm or other damage, acts as a critical defensive mechanism for organisms, alerting them to potential danger (Walters and De C Williams, 2019). It is characterized by two predominant types: nociceptive and neuropathic, with the former arising from noxious stimulation of sensory neurons called nociceptors. These neurons respond to various stimuli, including harsh mechanical forces, extreme thermal conditions, and chemical triggers (Tracey, 2017). The last few decades have seen significant strides in understanding pain's complex biology, unraveling the intricate web of neural pathways, neurotransmitters, receptors, and modulatory systems involved in pain perception and response (Vardeh et al., 2016; Walters, 2018).

Conventional analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) and opioids have long been the cornerstone of pain management, especially for inflammation-related and severe pain. Despite their effectiveness, the adverse effects associated with long-term NSAID use—such as gastrointestinal complications—and the serious side effects of opioids, including dependency and respiratory depression, underscore the urgent need for safer, non-addictive pain relief alternatives (Wang et al., 2014).

Amidst this backdrop, polyphenolic compounds, particularly flavonoids, have garnered attention for their therapeutic potential across various health conditions, including their role in cancer therapy, blood pressure regulation, liver protection, and diabetes control (Alqudah et al., 2023a; Li et al., 2016; Xue et al., 2019). A flavonoid of interest, homoeriodictyol (Fig. 1), presents a promising therapeutic profile (Islam et al., 2020). Abundant in certain plants, homoeriodictyol has been recognized for its antioxidant (Miyake et al., 2000), anti-inflammatory (Walker et al., 2016), and antitumor (Saquib et al., 2020) properties. It has been particularly noted for its ability to activate the Nrf2 pathway, which plays a pivotal role in cellular defense mechanisms against oxidative stress, as evidenced by its protection of endothelial cells from H_2O_2-induced damage—a process highly dependent on Nrf2 pathway activation (Shen et al., 2018).

This study explores the antinociceptive potential of homoeriodictyol, a compound yet to be extensively studied in the context of pain modulation. The research specifically focuses on assessing the efficacy of homoeriodictyol as a pain modulator through a series of nociception models in adult male mice. The objectives are to elucidate the effects of homoeriodictyol on pain modulation and to evaluate its potential as a contributor to new analgesic development. The investigation aims to advance understanding of the therapeutic actions of this flavonoid, potentially paving the way for innovative and safer alternatives in pain management. Such alternatives could offer significant benefits over existing pharmacotherapies, particularly in terms of reduced risk and side effects. The conclusions drawn from this study are anticipated to not only validate the hypothesis regarding homoeriodictyol's antinociceptive properties but also to align with the broader implications suggested by the title, thereby contributing valuable insights into pain management strategies.

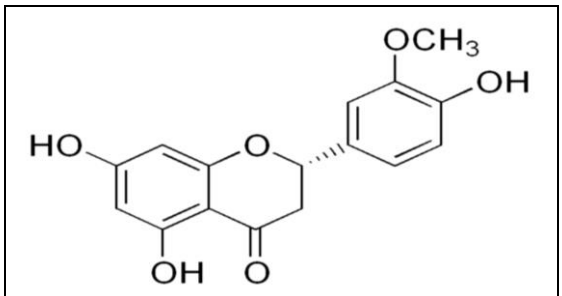

Figure 1. Chemical structure of homoeriodictyol.

MATERIAL AND METHODS

Experimental animals

Adult male Swiss albino mice weighing 24–28 grams were used for this study. They were sourced from the Animal House Unit of Hashemite University and kept in a 21 ± 1°C environment with a 12-hour light/dark cycle. Food and water were provided ad libitum. To reduce stress, the mice were acclimated to the lab an hour before testing. Two blind observers monitored the animals during the tests in a soundproof room to avoid bias. All animal experiments conducted during the study adhered to the regulations and guidelines of the Ethics Committee for Animal Experiments at Hashemite University, Jordan (IRB number: 15/8/2021/2022, 15/03/2021). The care and handling of the animals followed the ethical standards outlined by the International Association for the Study of Pain concerning the appropriate and ethical utilization of animals in pain research. Procedures that may cause more than momentary or slight pain or distress to animals should be performed with appropriate sedation, analgesia, or anesthesia, unless the procedure is justified for scientific reasons.

Acetic acid-induced abdominal constriction test

Mice were methodically allocated into six distinct groups to receive intraperitoneal injections, adhering to the methodology established by Koster et al. (1959).

The first group, serving as the control, was administered a solution comprising 5% DMSO and 95% water. The subsequent four groups were treated with varying concentrations of homoeriodictyol, specifically at doses of 50, 100, 150, and 200 µg/kg, each prepared in the vehicle solution. Additionally, another group was treated with 100 mg/kg of acetylsalicylic acid (ASA, Sigma-Aldrich, A5376). These dosages were selected based on insights garnered from preliminary studies. Post-treatment, each mouse was injected with a 0.6% acetic acid solution at a volume of 10 mL/kg, 60 minutes later. The subsequent writhing responses were meticulously observed and recorded over a 30-minute period following the acetic acid administration. Writhing inhibition percentage (PIW) was calculated as [1].

$$\text{Inhibition (\%)} = \frac{C - T}{C} \times 100 \quad [1]$$

Where C is control writhing and T is treated writhing.

The effective dose 50 (ED_{50}) for homoeriodictyol in the acetic acid-induced nociception model was calculated by plotting the doses against the percentage of writhing inhibition observed in mice and determining the dose at which there was a 50% increase in the percentage of writhing compared to the control group.

Hot plate test

Eight groups of mice were subjected to different treatment protocols. The control group was given 5% DMSO, while four other groups received varying doses of homoeriodictyol, specifically 50, 100, 150, and 200 µg/kg. Another group was treated with 5 mg/kg of morphine, obtained from Sigma (product M8777). To assess the efficacy of these treatments, reaction times were measured on a hot plate maintained at 55 ± 5 °C, both before treatment and 60 minutes afterward. The percentage increase in reaction time over the baseline was calculated using the formula [2], where 'A' represents the post-treatment time and 'B' signifies the pre-treatment time, as outlined in the study by Alqudah et al. (2023b).

$$\text{Increase (\%)} = \frac{A - B}{B} \times 100 \quad [2]$$

The ED_{50} for homoeriodictyol was determined by analyzing the dose-response curve plotted with the doses against the percentage increase in reaction time over the baseline, identifying the dose where the reaction time was increased by 50%.

Formalin-induced paw-licking test

In this experiment, nine groups of mice were designated to receive various treatments to investigate pain response mechanisms. The first group, serving as the vehicle control, was administered distilled water containing 5% DMSO. Groups two through five were treated with homoeriodictyol at 50, 100, 150, and 200 µg/kg, respectively. The sixth group received 5 mg/kg of morphine, while the seventh group was treated with 100 mg/kg of ASA (acetylsalicylic acid).

Further exploring the involvement of the opioidergic system, following a methodology described by Tjølsen et al. (1992), two additional groups were included: group eight received naloxone hydrochloride, a nonselective opioid receptor antagonist, at a dose of 5 mg/kg (administered intraperitoneally) 15 minutes prior to homoeriodictyol administration (200 µg/kg). Group nine similarly received naloxone hydrochloride (5 mg/kg, administered intraperitoneally) 15 minutes before morphine treatment (5 mg/kg).

All treatments were administered via intraperitoneal injection. To induce pain, each mouse received an injection of 20 µL of 2.5% formalin from Sigma Aldrich, Merck, into the subplantar region of the right hind paw approximately 60 minutes post-treatment. The nociceptive response was assessed by measuring the duration each mouse spent licking the formalin injection site.

Licking times were recorded for two distinct phases: the first phase (0–5 minutes post-formalin injection) representing the early (neurogenic) phase and the second phase (15–30 minutes post-injection) representing the late (inflammatory) phase. The percentage of licking inhibition (PIL) was then calculated using a designated formula [3], as detailed in Alqudah et al. (2022).

$$\text{PIL} = \frac{\text{Licking time (C)} - \text{Licking time (T)}}{\text{Licking time (C)}} \times 100 \quad [3]$$

Where C is control licking time, and T is treated licking time.

For the formalin-induced pain experiment, the ED_{50} of homoeriodictyol was calculated from the curve showing different doses against the percentage inhibition of licking time during both the neurogenic and inflammatory phases, with the ED_{50} being the dose at which licking time was reduced by 50%.

Capsaicin-induced paw-licking assessment

This assessment was conducted to evaluate the potential pain-blocking effects of homoeriodictyol on TRPV1 receptors, as detailed in Gammoh et al. (2023). For this purpose, thirty-six mice were divided into six

groups, each receiving treatments via intraperitoneal injection. The first group, designated as the control, was administered a solution of 5% DMSO in distilled water. The subsequent four groups were treated with homoeriodictyol at escalating doses of 50, 100, 150, and 200 µg/kg, respectively. The final group received an injection of the TRPV1 blocker, capsazepine, at a concentration of 0.17 mmol/kg.

To assess the pain response, one hour post-treatment, each mouse was administered 20 µL of capsaicin (1.6 µmol per paw) into the right hind paw. Following this, the pain response was observed by timing the licking or biting behaviors of the mice at the capsaicin application site for a duration of five minutes. This method provided a measure of the efficacy of homoeriodictyol and capsazepine in mitigating the pain response triggered by capsaicin. The ED_{50} of homoeriodictyol was computed by plotting its doses against the reduction in time spent licking or biting post-capsaicin injection, with the ED_{50} identified as the dose leading to a 50% decrease in this pain response.

Glutamate-induced paw-licking evaluation

The evaluation was focused on determining the effectiveness of homoeriodictyol in inhibiting pain, specifically through its action on glutamatergic receptors, as referenced in Meotti et al. (2010). To facilitate this study, five groups were established, each consisting of six mice. The administered treatments for these groups were as follows: the control group received an intraperitoneal injection of 5% DMSO, while the remaining four groups were treated with homoeriodictyol at incremental doses of 50, 100, 150, and 200 µg/kg, also delivered intraperitoneally.

To evaluate the pain response, each mouse was injected with 20 µL of glutamate into the lower side of the right hind paw sixty minutes post-treatment. In the 15 minutes that followed, the behavior of the mice was closely observed. The duration of licking and biting at the site of the glutamate injection was meticulously recorded for each mouse. This observation period was crucial for assessing the potential analgesic effects of homoeriodictyol against glutamate-induced pain.

The ED_{50} for homoeriodictyol was determined by creating a dose-response curve using the doses and the corresponding decrease in licking and biting behavior post-glutamate injection, defining the ED_{50} as the dose at which there was a 50% reduction in these behaviors.

Statistical analysis

GraphPad Prism 5 was used for data analysis. Data normality was confirmed with the Kolmogorov-Smirnov test. Results are shown as mean ± SEM. Group differences were evaluated using one-way ANOVA and Tukey's posthoc test, with $p<0.05$ as the significance threshold.

RESULTS

Homoeriodictyol mitigates acetic acid-induced writhing

Upon intraperitoneal injection, homoeriodictyol at 100, 150, and 200 µg/kg doses markedly lowered the writhing responses to acetic acid in mice compared to the vehicle control, as demonstrated in Fig. 2. The analgesic effect showed a dose-responsive relationship ($p<0.05$), with the strongest dose achieving a 52.4% reduction in writhing episodes ($p<0.001$). In contrast, the reference drug, ASA at 100 mg/kg, led to a 68.3% decrease in writhing. The effective dose of homoeriodictyol was 122.5 ± 32.6 mg/kg.

Homoeriodictyol enhances latency in hot plate test

When homoeriodictyol was administered at increments of 50 to 200 µg/kg, there was a significant and dose-dependent increase in the time it took for mice to respond to thermal pain on a hot plate, as shown in Fig. 3. The 200 µg/kg dose resulted in a 65.8% increase in latency time ($p<0.001$). Morphine, as a reference, yielded a 97.3% increase. The addition of naloxone, an opioid receptor blocker, prior to homoeriodictyol or morphine significantly diminished the latency time increase caused by both treatments ($p<0.001$), suggesting the involvement of opioid pathways. The ED_{50} of homoeriodictyol was 99.6 ± 29.3 mg/kg.

Homoeriodictyol alleviates pain in the formalin test

Administering homoeriodictyol in doses of 100, 150, and 200 µg/kg significantly decreased the licking times in both the early and late phases after formalin injection, following a dose-dependent pattern (Fig. 4). Morphine also significantly reduced licking times in both phases, whereas ASA did not affect the early phase but did significantly reduce the late phase licking time ($p<0.001$). When naloxone was used prior to homoeriodictyol or morphine, it notably increased the licking times compared to treatments without naloxone ($p<0.001$), highlighting the role of the opioidergic system in the pain-relief mechanism of both drugs. The ED_{50} of homoeriodictyol was 115.4 ± 22.8 mg/kg.

Reduction of licking time with homoeriodictyol post-capsaicin

The study investigated homoeriodictyol pain-relief effects on the vanilloid system, noting that doses ranging from 50 to 200 µg/kg significantly lessened licking time after capsaicin injection, indicating a dose-responsive effect ($p<0.01$), as illustrated in Fig. 5. The TRPV1 receptor blocker capsazepine also significantly decreased licking time, suggesting that homoeriodictyol antinociceptive actions are mediated through the vanilloid system. The ED_{50} of homoeriodictyol was 52.3 ± 12.7 mg/kg.

Homoeriodictyol reduces licking time post-glutamate

Following glutamate injection, homoeriodictyol administered at 100, 150, and 200 µg/kg significantly reduced paw licking times ($p<0.001$), with the antinociceptive effect being dose-dependent ($p<0.05$), as depicted in Fig. 6. This indicates homoeriodictyol potential in mitigating glutamate-induced pain responses. The ED_{50} of homoeriodictyol was 147.2 ± 26.6 mg/kg.

DISCUSSION

The investigation into the antinociceptive efficacy of homoeriodictyol presented in this study contributes to a growing body of evidence supporting the analgesic potential of flavonoids. The findings of this study suggest that homoeriodictyol exerts a significant dose-dependent reduction in nociceptive behavior across multiple pain models, indicative of its broad-spectrum analgesic activity. This is in line with previous studies highlighting the anti-inflammatory and antioxidative effects of flavonoids, which have been associated with reduced nociception (Kumar and Pandey, 2013).

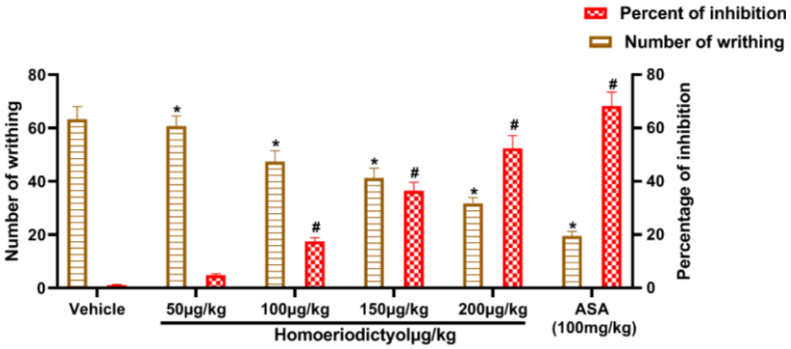

Figure 2. The impact of homoeriodictyol on writhing in mice induced by a 0.6% acetic acid solution.

Data represent mean ± standard error of mean (SEM) (n = 6). The study involved six mice, each of which received different treatments: 5% DMSO (considered the vehicle), homoeriodictyol. at various doses (50, 100, 150, 200 µg/kg i.p.), or acetylsalicylic acid (ASA) at a dose of 100 mg/kg. The results demonstrated a remarkable reduction in the number of writhing episodes when compared to the vehicle, with a significant difference (*$p<0.001$). Additionally, the percentage of inhibition induced by homoeriodictyol. was also significantly distinct from the vehicle, indicated by (#$p<0.001$).

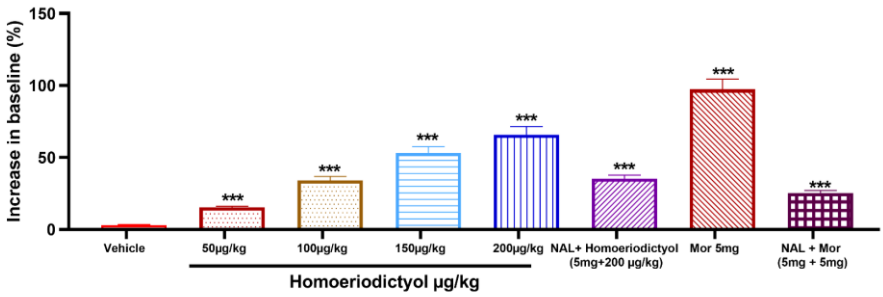

Figure 3. The impact of homoeriodictyol on mice was evaluated using the hot plate test.

Data represent mean ± standard error of mean (SEM) (n = 6). Statistical analysis revealed a significant difference when comparing homoeriodictyol. to the vehicle (5% DMSO), with a high level of significance (***$p<0.001$). Furthermore, the effect of 200 µg/kg homoeriodictyol. and 5 mg/kg morphine was blocked by naloxone (NAL), with a very strong level of significance (###$p<0.001$). Here, $ signifies the difference between the combination of Nal + Mor and Mor alone. (NAL: naloxone, Mor: morphine).

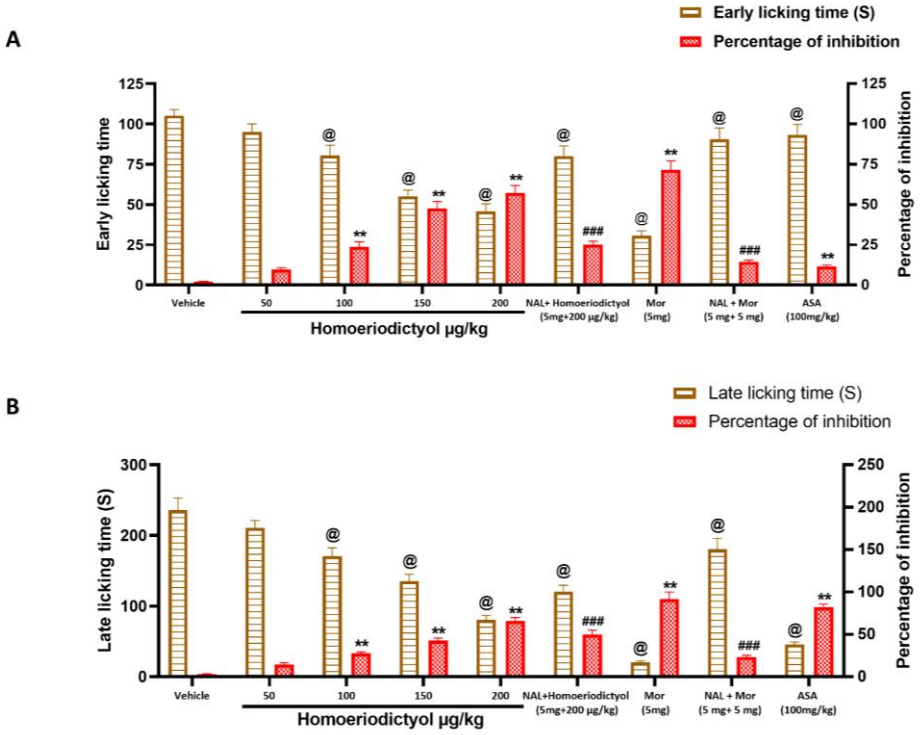

Figure 4. Influence of homoeriodictyol on both the early **(A)** and late **(B)** phases of paw-licking behavior induced by a 2.5% formalin solution in mice was investigated.

Data represent mean ± standard error of mean (SEM) (n = 6). The mice received various injections, including 5% DMSO (used as the vehicle), homoeriodictyol. (at doses of 50, 100, 150, and 200 µg/kg, i.p.), morphine (Mor) (at a dose of 5 mg/kg, i.p.), or acetylsalicylic acid (ASA) (at a dose of 100 mg/kg, i.p.). Naloxone (NAL) was administered at a dose of 5 mg/kg, i.p., 15 minutes before the injection of homoeriodictyol. (200 µg/kg) or Mor (5 mg/kg, i.p.). The results demonstrated a highly significant difference (**p<0.001) in the percentage of inhibition compared to the vehicle. Additionally, a significant difference (@ p<0.001) was observed in the licking time compared to the vehicle. Furthermore, a very significant difference (###p<0.001) was found between the combination of homoeriodictyol. + Nal and homoeriodictyol. (200 µg/kg) alone, indicated by ###. Also, $ denotes a significant difference between the combination of Nal + Mor and Mor alone.

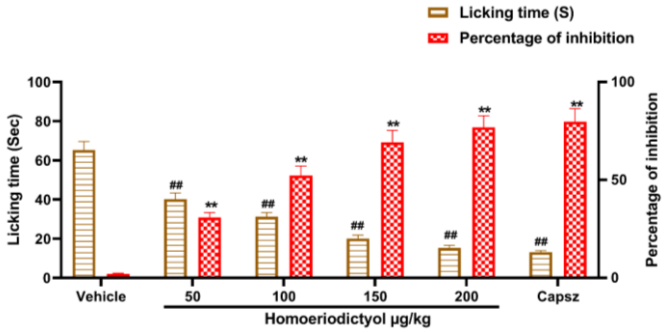

Figure 5. The impact of homoeriodictyol on paw licking induced by capsaicin in mice.

Data represent mean ± standard error of mean (SEM) (n = 6). The mice were divided into five groups, each consisting of six male mice. They were administered with different substances: 5% DMSO (used as a vehicle), homoeriodictyol at doses of 50, 100, 150, and 200 µg/kg (i.p.), or the capsaicin antagonist capsazepine (Capsz, at a dose of 0.17 mmol/kg, i.p.). After 60 minutes, the mice were exposed to capsaicin, and the duration of licking was recorded. The results indicated a significant reduction (**p<0.01) in the percentage of inhibition compared to the control group, signifying the effectiveness of homoeriodictyol. Moreover, there was also a notable reduction (##p<0.01) in the licking time compared to the control group, highlighting the impact of homoeriodictyol. in decreasing the response to capsaicin.

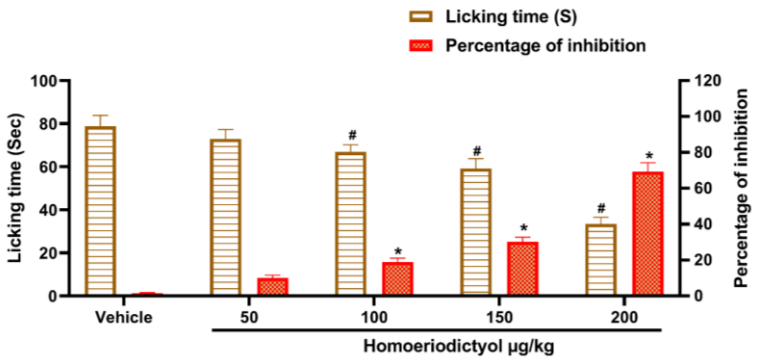

Figure 6. The effect of homoeriodictyol on paw licking induced by glutamate in mice.

Data represent mean ± standard error of mean (SEM) (n = 6). The mice were divided into five groups, each consisting of six male mice. These groups were administered intraperitoneally with either 5% DMSO (used as a vehicle) or homoeriodictyol. at doses of 50, 100, 150, and 200 µg/kg. After a 60-minute interval, 20 µL of glutamate was administered intraplantarly into the right hind paw, and the duration of licking was recorded. The results showed a highly significant reduction (*p<0.001) in the percentage of inhibition when compared to the control group, indicating the effectiveness of homoeriodictyol. in mitigating the response to glutamate. Additionally, there was a substantial reduction (#p<0.001) in licking time compared to the control group, underscoring the impact of homoeriodictyol. in reducing the pain response to glutamate-induced paw licking.

The reduction of writhing responses by homoeriodictyol in the acetic acid-induced assay aligns with the known actions of NSAIDs and implicates the inhibition of peripheral pain mechanisms, possibly via COX pathways (Smith, 2005). However, unlike NSAIDs, homoeriodictyol did not produce observable adverse effects in gastrointestinal tissues, which is a significant finding given the common gastrointestinal complications associated with NSAID therapy (Wallace, 2001).

In the hot plate model, the increased latency to thermal stimuli provided by homoeriodictyol is suggestive of central analgesic effects, potentially involving opioidergic pathways, as demonstrated by the reversal of analgesia upon naloxone administration (Stein, 2016). These results are novel for a flavonoid compound and may indicate a unique interaction with opioid receptors or endogenous opioids, warranting further molecular investigation.

The compound's efficacy in both phases of the formalin test suggests that homoeriodictyol can modulate pain through both neurogenic and inflammatory pathways. This bimodal action is not typically observed with conventional opioids, which are less effective against inflammatory pain, hence positioning homoeriodictyol as a potentially versatile analgesic agent (Coderre and Melzack, 1992).

Moreover, the attenuation of capsaicin-induced responses by homoeriodictyol points to an antagonistic effect on TRPV1 receptors, which are known to mediate nociceptive signals, especially those related to inflammatory and neuropathic pain (Caterina et al., 2000). The compound's action on glutamate-induced nociception further underscores its potential role in modulating neurotransmitter systems involved in pain signaling (Fundytus, 2001).

The implications of these findings are substantial. With the opioid crisis and the limitations of current analgesics, there is a clear need for new pain management strategies. Homoeriodictyol's antinociceptive properties, coupled with its safety profile, make it a promising candidate for drug development. Nevertheless, translation from animal models to clinical application requires careful consideration of pharmacokinetics, bioavailability, and the potential for human side effects, which have yet to be thoroughly investigated (Silberberg et al., 2006).

Future research should aim to clarify the molecular mechanisms underlying homoeriodictyol's antinociceptive effects, particularly its interactions with opioid receptors and the implications for opioid-sparing analgesic strategies. Additionally, studies focusing on the bioavailability and metabolism of homoeriodictyol will be critical to its development as a therapeutic agent.

CONCLUSION

This study adds valuable insight into the analgesic potential of flavonoids and paves the way for further research into homoeriodictyol as a novel, non-opioid analgesic. The findings of this study support the continued exploration of natural compounds in the search for effective and safer pain management options.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Al-Bzour M	Bsieso Y	Gammoh O	Alqudah M	Qnais E	Wedyan M	Alqudah A
Concepts or ideas	x						x
Design	x				x		
Definition of intellectual content			x				
Literature search		x					
Experimental studies			x				
Data acquisition				x			
Data analysis						x	
Statistical analysis						x	
Manuscript preparation	x						x
Manuscript editing							x
Manuscript review	x	x	x	x	x	x	x

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