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# POSSIBLE INVOLVEMENT OF SEROTONIN RECEPTORS AND NO/CGMP PATHWAY IN THE ANTINOCICEPTIVE EFFECT OF GERANIUM ESSENTIAL OIL

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***Background:*** *Previous studies have shown that Geranium essential oil (GEO) has anti-inflammatory and antinociceptive effects . The present study was performed to determine the possible mechanism of antinociception of GEO in an animal model.* ***Methods:*** *Formalin test in male Swiss mice (25–30 g) was conducted to assess the antinociceptive effect. Antagonists of several receptors involved in pain pathway including prazosin, yohimbine, propranolol, naloxone, sulpiride, haloperidol, ondansetron, cyproheptadine as well as drugs affecting NO/cGMP pathway (arginine, L-NAME, Methylene blue, tadalafil and glibenclamide) were administered 30 minutes before the administration of GEO. Thirty minutes later formalin was injected into the subplantar space of the right hind paw and the time spent for paw licking was recorded 0-5 (acute phase) and 20-40 minutes (chronic phase) after formalin as pain index.* ***Results:*** *GEO (25, 50, and 100 µL/kg) showed antinociceptive activity in formalin test. Pretreatment of mice with naloxone, prazosin, yohimbine, propranolol, sulpiride, and ondansetron failed to inhibit GEO-induced antinociceptive effect indicating that opioid, α1-, α2- and β-adrenergic, $D_2$ dopamine and serotonin 5-$HT_3$ receptors are not involved. Cyproheptadine significantly inhibited the GEO effect in the chronic phase of formalin test indicating that 5-$HT_2$ serotonin and/or $H_1$ histamine receptors might contribute to the antinociceptive effect of GEO. Results also showed that drugs affecting NO/cGMP altered GEO effect.* ***Conclusions:*** *The findings revealed that serotonin (possibly 5-HT2) and/or histamine $H_1$ receptors as well as NO/cGMP pathway contribute to the antinociceptive effect of GEO.*

***Keywords:*** *Analgesics; antinociception; Formaldehyde; Geranium; Mice; Pain Measurement; Pelargonium graveolens; Volatile Oils*

## INTRODUCTION

*Pelargonium graveolens* (rose geranium) is a well-known plant of Geraniaceae family[1]. Biological and pharmacological effects of geranium essential oil (GEO) have been extensively investigated and numerous effects including antimicrobial[2,3], antifungal[4], antioxidant[3,5], anti-inflammatory [6,7], anticancer[8] and hypoglycemic effects[9] have been reported for GEO. The oil is also used in the treatment of heavy menstrual flows, hemorrhoids and dysentery[10].

Bastani et al. (2019) reported the beneficial effect of GEO on inflammatory bowel disease in a rat model[11]. The plant hydroalcoholic extract showed protective effects against acetaminophen-induced kidney damage[12]. Heydari and Mirazi (2016) reported that the extract prepared from leaves of *P. graveolens* showed antinociception in writhing and hot plate models[13]. Also, geraniol, a monoterpene alcohol found in GEO and other essential oils reduced paw licking time in formalin and glutamate tests[14].

Pain signaling is very complex and according to previous studies, several neurotransmitters and receptors, enzymes and ion channels play a role in nociceptive signaling. Opioid, $\alpha_2$-adrenergic, dopamine and serotonin (especially $5HT_3$ and $5HT_2$) receptors as well as nitric oxide pathway are among the

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most important components involved in pain modulation[15-19]. To the best of our knowledge, there is no study about the mechanism of GEO-induced antinociceptive effect; therefore this study was aimed to find out the possible mechanism(s) using various antagonists and inhibitors of nociceptive signaling.

## MATERIALS AND METHODS

### Drugs

Geranium essential oil was a gift from Tabib Daru Company (Kashan, Iran). Tadalafil and cyproheptadine were gifts from Farabi and Raha Pharmaceutical Companies (Isfahan, Iran) respectively. Ondansetron (Tehran Chemie Pharmaceutical Co., Tehran, Iran), propranolol and naloxone (Toliddaru, Tehran, Iran) were also used. Other chemicals including prazosin, yohimbine, haloperidol, sulpiride, L-NAME, arginine, methylene blue and glibenclamide were purchased from Sigma Aldrich Co. (St Louis, MO, USA).

### Animals

Male Swiss mice (25-30 g, 6 weeks old) were kept in standard conditions of humidity, temperature and light/dark cycle in the animal house of the School of Pharmacy (Isfahan, Iran). One week before the experiments, animals were transferred to the laboratory to acclimate to the environmental conditions. They had free access to food and water. Six mice were housed in each cage and all the animal experiments were performed according to guidelines for the care and use of laboratory animals provided by the National Ethical Committee (Iran) (Ethics code: IR.MUI.RESEARCH.REC.1401.035).

### Experimental design

Firstly, three doses of GEO were selected according to the previous reports[20] and its antinociceptive activity was tested in the formalin test and then the most suitable dose was selected for mechanistic studies. To find out the mechanism of action of GEO, antagonists or enzyme inhibitors were injected thirty minutes before injection of GEO and 30 minutes later 20 µL of formalin solution (2.5% v/v in saline) was injected into the subplantar space of the right hind paw of mice. The paw licking time was an index of pain in both acute and chronic phases after formalin injection[21,22].

### Groups of animals

A total of 102 mice (17 groups, 6 mice each) were grouped as follows:

Group 1: Control group received vehicle (10 mL/kg, 1% tween 80 in saline); Groups 2-4: GEO (25, 50 and 100 µL/kg); Group 5: Prazosin (2 mg/kg); Group 6: Yohimbine (5 mg/kg); Group 7: Propranolol (2 mg/kg); Group 8: Cyproheptadine (2 mg/kg); Group 9: Ondansetron (2 mg/kg); Group 10: Naloxone (5 mg/kg); Group 11: Haloperidol (1 mg/kg); Group 12: Sulpiride (20 mg/kg);

Group 13: Arginine (100 mg/kg); Group 14: L-NAME (20 mg/kg); Group 15: Methylene blue (5 mg/kg); Group 16: Tadalafil (2 mg/kg); Group 17: Glibenclamide (10 mg/kg). Animals in groups 5 to 17 received GEO (50 µL/kg) thirty minutes after above treatments. Doses of drugs were selected based on previous studies[23].

### Statistical analysis

Results are expressed as mean ± SEM. To analyze the obtained data, one-way analysis of variance (ANOVA) and Tukey post hoc tests were used. The differences were considered significant for *p*-values less than 0.05. SPSS package (version 23) and Excel 2020 were used for statistics and preparing graphs respectively.

## RESULTS AND DISCUSSION

### Antinociceptive effect of three different doses of GEO

In the acute phase, GEO at a dose of 25 µL/kg did not exhibit a significant antinociceptive effect, while doses of 50 and 100 µL/kg showed significant antinociception ($p = 0.035$ and $p < 0.001$ respectively). All three doses of GEO demonstrated significant effect in the chronic phase **(Fig. 1)**.

### Effect of adrenergic receptor antagonists on GEO antinociceptive effect

Pretreatment of mice with prazosin, yohimbine and propranolol did not produce any significant alteration of GEO-induced nociception in both phases of formalin test **(Fig. 2)**.

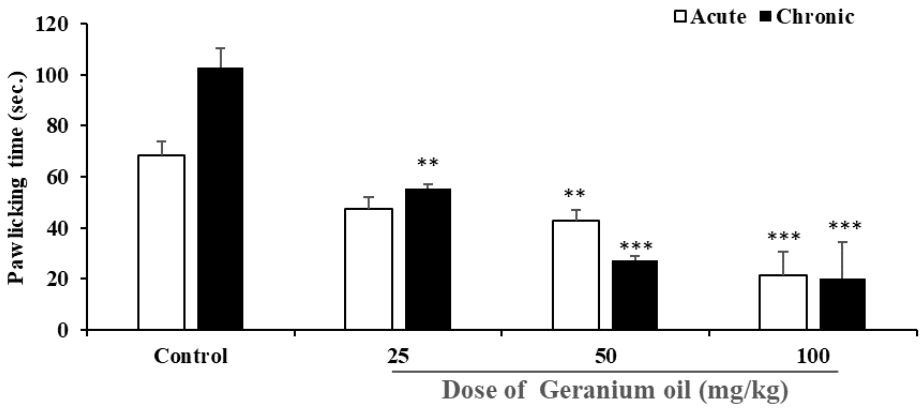


**Fig. 1:** Antinociceptive effect of geranium oil in formalin test.
Geranium oil (25, 50 and 100 µL/kg) was injected i.p. and thirty minutes later formalin (20 µL, 2.5% v/v in saline) was injected into the subplantar space of the right hind paw. ** $p < 0.01$ and *** $p < 0.001$ compared to vehicle-treated group (control).

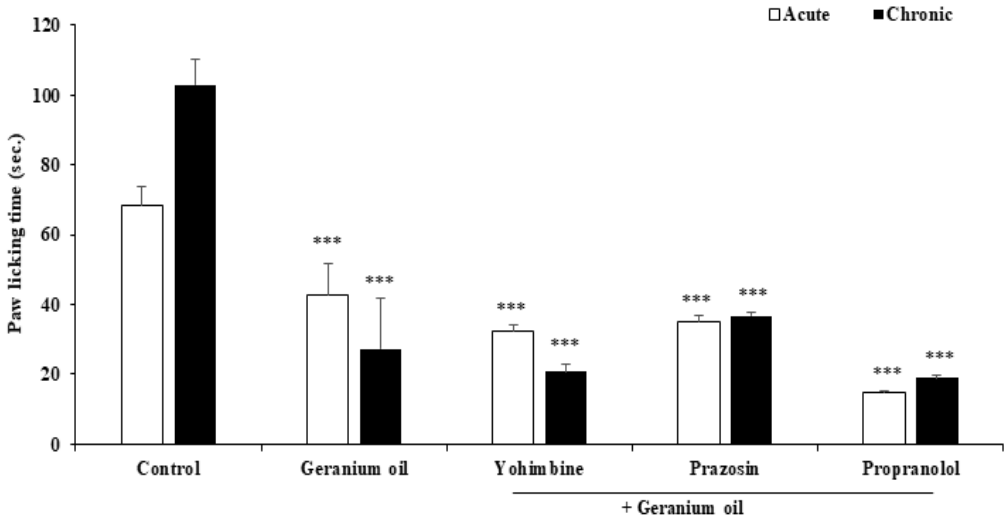


**Fig. 2:** Effect of adrenergic receptor antagonists on geranium oil-induced antinociceptive effect.

Prazosin (2 mg/kg), yohimbine (5 mg/kg) and propranolol (2 mg/kg) were injected (i.p.) 30 minutes prior to geranium oil (50 µL/kg, i.p.). Thirty minutes later, formalin (20 µL, 2.5% v/v in saline) was injected and the paw licking was recorded. *** indicates $p < 0.001$ compared to vehicle-treated group (control).

**Evaluation of ondansetron and cyproheptadine on antinociceptive effect of GEO**

In this experiment, pretreatment of mice with ondansetron as a selective $5HT_3$ antagonist did not inhibit GEO-induced reduction of formalin pain behavior in both phases. Cyproheptadine significantly ($p= 0.008$) inhibited GEO effect in the second phase and the paw licking time in GEO group and GEO+ cyproheptadine were 36.0 ± 4.7 and 50.5 ± 4.2 seconds respectively **(Fig. 3)**.

**The effect of naloxone on the antinociceptive effect of GEO**

As it is observed in **Fig. 4**, naloxone (5 mg /kg) as a well-known opioid receptor antagonist did not exhibit any significant change in the antinociceptive effect of GEO in both phases of formalin test.

**The effect of haloperidol and sulpiride on the GEO antinociception**

In the acute phase of formalin test, the paw licking time for control, GEO, sulpiride and haloperidol groups were 68.3 ± 5.4, 42.7 ± 4.3, 38.3 ± 4.2 and 13.5 ± 0.6 sec respectively. In the chronic phase, the respective times were: 102.8 ± 7.5, 27.3 ± 1.7, 12.0 ± 1.7 and 0.7 ± 0.3 second. The effect of sulpiride was insignificant in both phases, but haloperidol produced a significant ($p < 0.001$) potentiation of GEO effect in the chronic phase **(Fig. 5)**.

**The effect of NO/cGMP/$K_{ATP}$ pathway on the antinociceptive effect of GEO**

As seen in **Fig. 6**, in the acute phase, only L-NAME and glibenclamide potentiated GEO-induced antinociception. In the chronic phase, all tested drugs changed GEO-induced antinociceptive activity so that arginine and tadalafil significantly ($p < 0.001$) inhibited GEO-induced antinociceptive effect while L-NAME ($p= 0.047$), methylene blue ($p= 0.025$) and glibenclamide ($p < 0.001$) exerted a significant potentiation of the GEO effect.

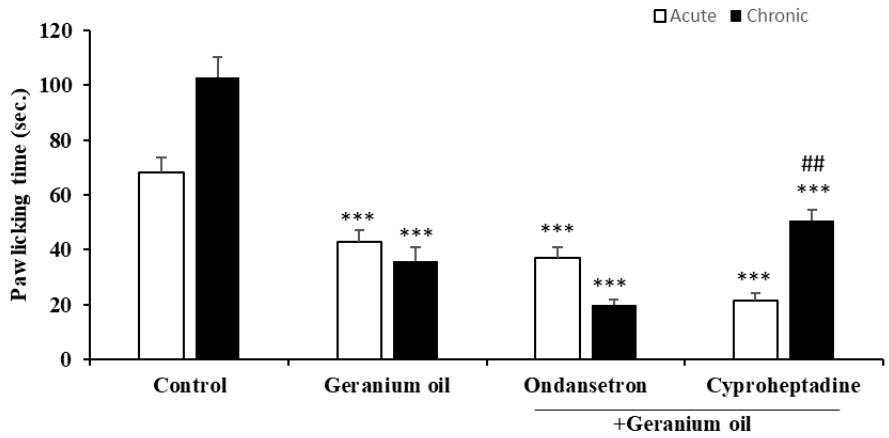


**Fig. 3:** Effect of ondansetron and cyproheptadine on geranium oil-induced antinociception. Geranium oil (50 µL/kg, i.p.) was administered thirty minutes after i.p. injection of ondansetron (2 mg/kg) and cyproheptadine (2 mg/kg). Thirty minutes later, formalin (20 µL, 2.5% v/v in saline) was injected and the paw licking was recorded. *** indicates $p < 0.001$ compared to vehicle-treated group (control). ## $p < 0.01$ compared to geranium oil alone.

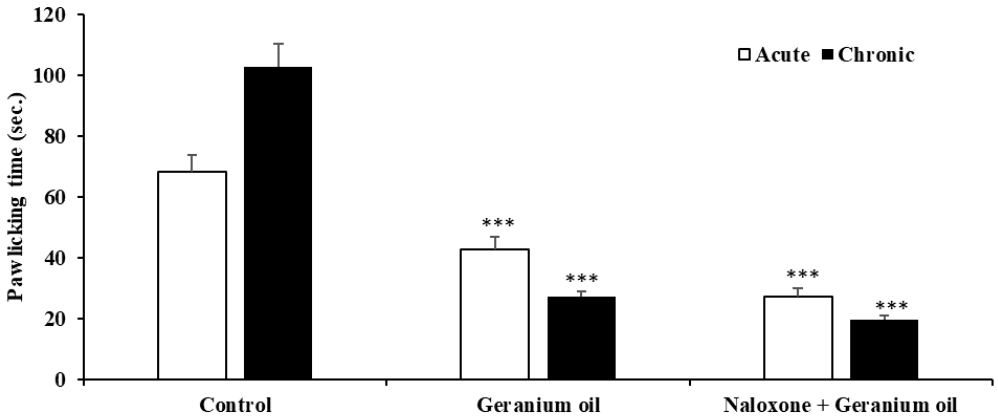


**Fig. 4:** Effect of naloxone on geranium oil-induced antinociceptive effect.

Naloxone (5 mg/kg) was injected (i.p.) 30 minutes prior to geranium oil (50 µL/kg, i.p.). Thirty minutes later, formalin (20 µL, 2.5% v/v in saline) was injected and the paw licking was recorded. *** indicates $p < 0.001$ compared to vehicle-treated group (control).

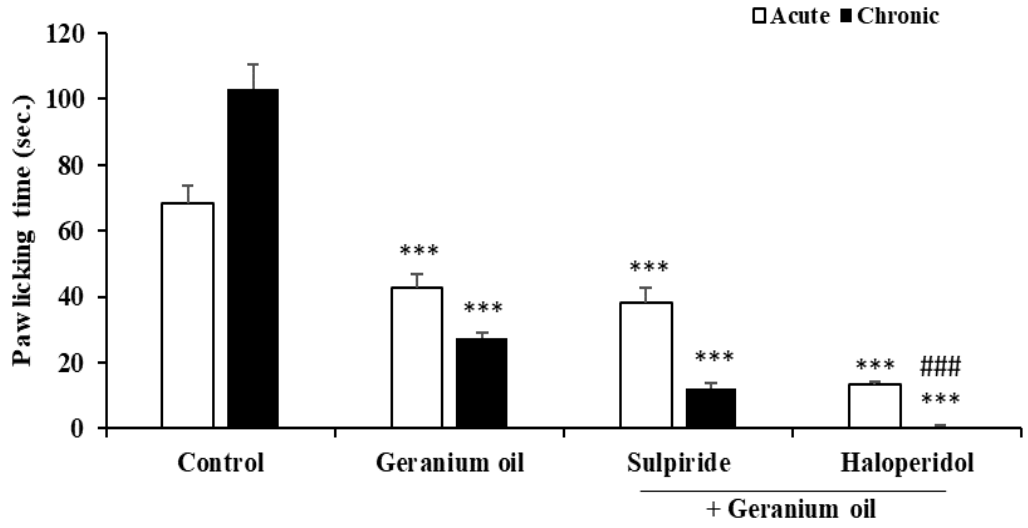


**Fig. 5:** Effect of sulpiride and haloperidol on geranium oil-induced antinociceptive effect. Sulpiride (20 mg/kg) and haloperidol (1 mg/kg) were injected (i.p.) 30 minutes prior to geranium oil (50 µL/kg, i.p.). Thirty minutes later formalin (20 µL, 2.5% v/v in saline) was injected and the paw licking was recorded. *** indicates $p < 0.001$ compared to vehicle-treated group (control). ### $p < 0.001$ compared to geranium oil alone.

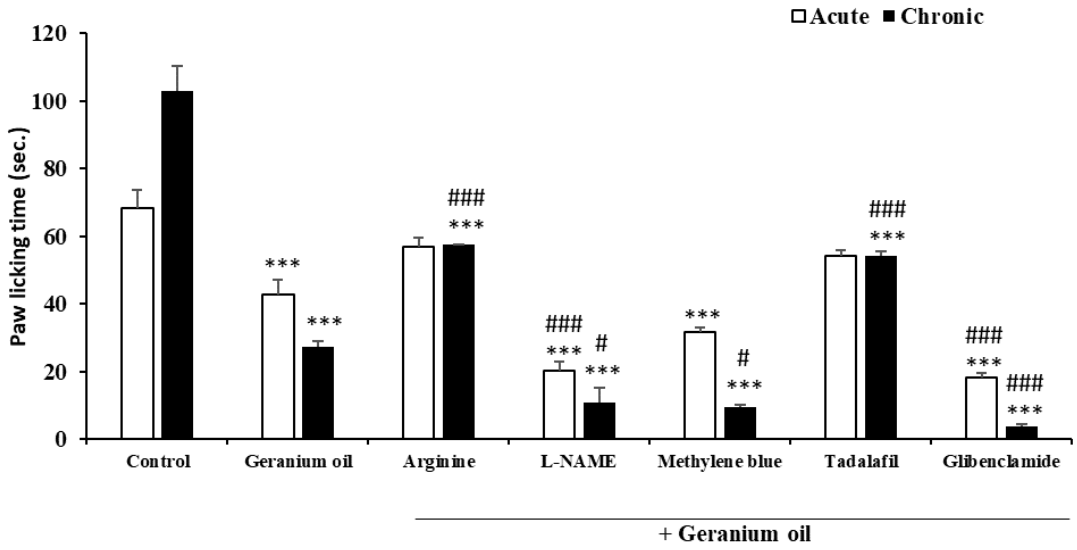


**Fig. 6:** effect of drugs of NO/cGMP signaling on geranium oil-induced antinociception.

Arginine (100 mg/kg), L-NAME (20 mg/kg), methylene blue (5 mg/kg), tadalafil (2 mg/kg) and glibenclamide (10 mg/kg) were administered 30 minutes before geranium oil (50 µL/kg, i.p.). Formalin (20 µL, 2.5% v/v in saline) was injected 30 minutes later and the paw licking time was recorded in acute (0-5 min.) and chronic (20-40 min.) phases. *** indicates $p < 0.001$ compared to vehicle-treated group (control). # $p < 0.05$ and ### $p < 0.001$ compared to geranium oil alone.

**Discussion**

In the present study, GEO dose-dependently demonstrated antinociceptive effect in both phases of formalin test. Also, the possible involvement of opioid, adrenergic, dopaminergic, serotonin receptors as well as NO/cGMP system in the antinociceptive effect of GEO was investigated. In formalin test, the acute (first) phase shows acute pain and the chronic (second) phase show an inflammatory pain[24]. Our results showed that GEO was effective in the suppression of both phases.

Different opioid receptors especially mu and kappa receptors are involved in pain signaling[25]. Pretreatment of animals with naloxone as a well-known and non-selective opioid antagonist did not affect GEO antinociception indicating that GEO is not associated with opioid receptor activation or release of endogenous opioids.

Previous studies have revealed the involvement of adrenergic receptors in nociceptive pathways [16,18]. Our findings showed that prazosin as an alpha-blocker agent partially inhibited GEO antinociceptive effect but this effect was insignificant. Yohimbine and propranolol could not exert any significant alteration in GEO effect indicating that alpha-2 and also beta adrenoreceptors are not involved in GEO-induced antinociceptive behavior.

According to the literature, serotonin is implicated in both central and peripheral components of analgesia. Stimulation of some brain areas like periaqueductal gray matter increases the spinal levels of serotonin. Also, among multiple serotonin receptors 5-HT3 and 5-HT2 subtypes have a more pronounced role in pain modulation[15,17,26].

To test the hypothesis that the antinociceptive effect of GEO could be due to its effect on serotonin receptors, cyproheptadine and ondansetron were used.

Ondansetron is a specific inhibitor of 5-$HT_3$ receptors. Although cyproheptadine is not a selective antagonist of serotonin receptors but Kapur et al. (1997) have reported that it exerts a potent antagonistic effect on $5HT_{2A}$, $5HT_{2B}$ and $5HT_{2C}$ subtypes[27]. Ondansetron could not prevent the antinociceptive activity of the oil and accordingly, the involvement of $5HT_3$ receptors was ruled out. Unlike ondansetron, cyproheptadine inhibited GEO-induced antinociceptive in the second phase of formalin test indicating the possible role of $5HT_2$ in the observed effect. Additionally cyproheptadine is an antagonist of histamine $H_1$ receptors. Previously Mobarakeh et al (2000) examined the pain threshold in histamine $H_1$ receptor knockout mice and reported that the receptor has a role in pain perception[28]. Therefor it might be concluded that serotonin $5HT_2$ and/or histamine $H_1$ receptors might involve in the cyproheptadine effect and further studies with more selective antagonists is needed to clarify the precise role of each receptor.

Dopamine is also an important neurotransmitter with five classes of receptors named D1 to D5. It has been documented that the facilitation of dopamine signaling is associated with antinociception in both writhing and formalin tests[29,30]. Some investigators have focused on the role of $D_1$ and $D_2$ receptors in pain modulation[19,31]. In our experiments, sulpiride as a selective $D_2$ receptor antagonist did not alter GEO-induced antinociception in both phases of formalin test indicating that this subtype is not implicated in GEO antinociception. Haloperidol as a non-selective dopamine antagonist could not reverse the antinociceptive effect of GEO in the first phase, but it surprisingly produced a significant potentiation of the GEO-induced antinociceptive effect in the second phase. Consistent with our findings Cendán et al (2005) showed that haloperidol has an antinociceptive effect in formalin test and proposed that this effect is probably due to its adrenergic-blocking activity[32].

In the present study, we also hypothesized that NO pathway may contribute to the GEO-induced antinociception. Our findings showed that arginine and tadalafil partially inhibited while L-NAME (inhibitor of NO synthase), methylene blue (inhibitor of guanylyl cyclase) and glibenclamide (inhibitor ATP-dependent K+ channel) potentiated the GEO antinociceptive activity. In conclusion, it seems that serotonin (especially 5-HT2 receptors) and NO/cGMP pathway play a role in the antinociceptive effect observed with GEO

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نشرة العلوم الصيدليـــة
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# المشاركة المحتملة لمستقبلات السيروتونين ومسار NO / CGMP في التأثير المضاد للألم لزيت إبرة الراعي العطرى

**ولي الله حجهاشمي* – ماجد بخشي**

**قسم علم الأدوية والسموم ، كلية الصيدلة والعلوم الصيدلانية ، جامعة أصفهان للعلوم الطبية ، أصفهان ، إيران**

**الخلفية** :أظهرت الدراسات السابقة أن زيت إبرة الراعي العطرى (GEO) له تأثيرات مضادة للالتهابات ومضادة للألم .أجريت الدراسة الحالية لتحديد الآلية المحتملة لمقاومة الألم في نموذج حيواني.

**الطرق** :تم إجراء اختبار الفورمالين في ذكور الفئران السويسرية 30-25)جم (لتقييم التأثير المضاد للألم . مضادات العديد من المستقبلات المشاركة في مسار الألم بما في ذلك برازوسين ، يوهيمبين ، بروبرانولول ، نالوكسون ، سلبيريد ، هالوبيريدول ، أوندانسيترون ، سيبروهيبتادين بالإضافة إلى الأدوية التي تؤثر على مسار ) NO / cGMPأرجينين ، L-NAME، الميثيلين الأزرق ، تادالافيل وجليبنكلاميد (تم إعطاؤها قبل 30دقيقة من إعطاءGEO. بعد ثلاثين دقيقة ، تم حقن الفورمالين في الفراغ الفرعي للمخلب الخلفي الأيمن وتم تسجيل الوقت المستغرق في لعق المخلب 5-0 (المرحلة الحادة) و 40-20 دقيقة (المرحلة المزمنة) بعد الفورمالين كمؤشر للألم.

**النتائج** :أظهر (25 GEO و 50و 100 ميكرولتر /كجم ) نشاطا مضادا للألم في اختبار الفورمالين .فشلت المعالجة المسبقة للفئران بالنالوكسون والبرازوسين واليوهيمبين والبروبرانولول والكبريبريد والأوندانسترون في تثبيط التأثير المضاد للألم الناجم عن GEO مما يشير إلى أن مستقبلات الأفيونيات و α1-و α2- و β-adrenergic و D2 الدوبامين والسيروتونين 5-HT3غير متورطة .يثبط سيبروهيبتادين بشكل كبير تأثير GEOفي المرحلة المزمنة من اختبار الفورمالين مما يشير إلى أن مستقبلات السيروتونين 5-HT2و /أو H1 قد تساهم في التأثير المضاد للألم ل .GEO أظهرت النتائج أيضا أن الأدوية التي تؤثر على NO / cGMPغيرت تأثير .GEO

**الاستنتاج** :كشفت النتائج أن السيروتونين ربما 5-HT2 و/ أو مستقبلات الهيستامين H1بالإضافة إلى مسار NO / cGMPيساهم في التأثير المضاد للألم لـ .GEO