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Royal Jelly as A Natural Analgesic and Antipyretic: Experimental Insights and PGE2 Modulation

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Abstract

PROSTAGLANDIN E2 (PGE2) plays a crucial role in pain and fever pathways, sensitizing nociceptors and regulating hypothalamic set points during inflammation. This study evaluates the analgesic and antipyretic effects of Royal Jelly, a nutrient-rich secretion from honeybees, in Wistar rats and Swiss albino mice, comparing its effects to those of Ibuprofen, Paracetamol, and Celecoxib. Royal jelly at a high dose of 200 mg/kg showed significant analgesic effects using hot plate technique, achieving 95.31% pain inhibition at 30 minutes and 37.53% at 60 minutes, outperforming Celecoxib. It also demonstrated a dose-dependent reduction in acetic acid-induced writhing, with inhibition rates of 42.01% for 100 mg/kg and 57.08% for 200 mg/kg, indicating both central and peripheral analgesic actions. Regarding antipyretic activity, royal jelly (200 mg/kg) produced a delayed yet sustained reduction in fever, achieving 68.57% inhibition at 2 hours and 85.71% at 3 hours post-treatment. In contrast, Paracetamol provided a rapid response with an 80.41% reduction at 1 hour. Royal jelly 's prolonged effects suggest it may modulate inflammatory mediators by suppressing prostaglandin biosynthesis. where our result shed the light on both ibuprofen (200 mg/kg) and high-dose royal jelly (200 mg/kg) significantly lowered PGE_2 levels, while the low dose (100 mg/kg) did not show any noted changes While its onset is slower than conventional drugs, its sustained action may offer therapeutic advantages. Future research should explore the synergistic potential of combining royal jelly with standard analgesics and antipyretics for improved clinical outcomes.

Keywords: Royal jelly, Pain, fever, analgesic, antipyretic, PGE2.

Introduction

Royal jelly is a highly nutritious secretion that is primarily used to feed queen bees and their larvae generated by worker honeybees. Because of its abundance of proteins, vitamins, minerals, and bioactive compounds, this unique substance is being studied in both conventional and alternative medicine [1]. Royal jelly has long been valued for its potential health benefits , such as its antibacterial, anti-inflammatory, and antioxidant properties [2].

The pharmacological applications of royal jelly have been better understood in recent years through scientific studies. Investigations exploring its potential for treating various types of diseases , including immune system disorders , cardiovascular ailments, and even some types of cancer, have been prompted by its diverse therapeutic effects [3]. Furthermore, royal jelly is becoming increasingly popular as a natural supplement to improve general health, promote healthy skin, and alleviate menopausal symptoms. Royal jelly stands out as a valuable ingredient in natural medicine, with

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significant prospects for pharmaceutical development and holistic health practices as researchers continue to examine its potential [4].

Previous studies have demonstrated that royal jelly contains numerous bioactive substances, such as proteins, lipids, vitamins, and minerals, have been shown in royal jelly which contribute to its pharmacological effects in earlier studies. Interestingly, these compounds have the ability to modulate inflammatory pathways, which reduces fever and pain caused on by various diseases. Royal jelly's anti-inflammatory activity is attributed to its ability to suppress pro-inflammatory cytokines and enzymes providing a natural alternative for the treatment of inflammatory conditions [5].

Given the increasing interest in natural remedies and the growing prevalence of chronic inflammatory diseases, royal jelly's analgesic and antipyretic properties offer exciting possibilities for developing new therapeutic strategies. As we explore its potential, understanding the mechanisms underlying these effects will be crucial for harnessing royal jelly's full pharmaceutical potential and integrating it into modern healthcare practices. The current study aimed to explore the antipyretic and analgesic properties of royal jelly as a natural approach to inflammation management.

Materials and Methods

Materials

The royal jelly for the experiment was obtained from beekeepers in the Giza region and was converted into a lyophilized form using a freezing dryer machine. Subsequently, the dried product was preserved in a dark glass container in a cool and dry place. Celecoxib was obtained from Sigma Aldrich Company (Darmstadt, Germany). Brewer's yeast was purchased from Angel Yeast Company, (Hubei, China).

Methods

Experimental animals and acute toxicity assessment

Female Swiss Albino mice (20-30 g) and Wistar rats (body weight: 140–170 g) were obtained from the National Research Centre (NRC) animal house in Cairo, Egypt. The rats were housed in metal cages at the (NRC) animal house under standard laboratory conditions, with ad libitum access to food and water. All experimental procedures and treatments were carried out in accordance with the US National Institutes of Health guidelines and the NRC Committee, Egypt's ethics protocol (Ethical permission ID: CU/F/16/21).

To assess the acute toxicity of royal jelly, 16 female Wistar rats were divided into two groups, each consisting of 8 rats. Royal jelly was administered orally to group 1, whereas equal volumes of distilled water were administered orally to group 2 as a control group. For 24 hours, all animals were continuously monitored for mortality. Additionally, all physical changes of mice including those to their skin, fur, circulatory system, and respiratory system were noted [6,7].

Analgesic, antipyretic effects of Royal jelly Central analgesic potentiality

The standard hot plate test was used to implement the in vivo pain induction. Each group consisted of five albino mice (20–25 g) of either sex. Mice were placed on a hot plate maintained at 52 ±1 °C for 30 minutes in order to undergo a thorough examination (7280 Ugo Basile Biological Research Apparatus Company, Comerio, Italy). El-Karim et al. (2021) earlier described the equipment. It consists of a hot plate that the rat was tested on. It consists of a 20 cm diameter metal hot plate surface that is set to 51–53°C. The latency to show nociceptive responses such as licking paws or jumping was measured 30-, 60-, 90-, and 120-minutes post-treatment. To avoid tissue injury, a maximum cutoff time of 15 seconds was established. Response latencies were recorded at 30, 60, 90, and 120 minutes post-treatment and he protection percentage was calculated using the following equation [8]

$$Protection\ \% = \frac{T1-T0}{T0}\ X\ 100$$

Where, T1: the mean latency time of the tested sample, T0: the mean latency time of the control.

Peripheral analgesic activity

Peripheral analgesic activity was assessed using the acetic acid-induced writhing test in mice. Each group consisted of six albino mice of either sex, weighing between 20 and 25 grams. One hour after oral administration of royal jelly at two different doses, as well as ibuprofen at 200 mg/kg body weight, each mouse received an intraperitoneal injection of 0.1 ml of 1% acetic acid solution. The control group received only distilled water. Beginning five minutes after the acetic acid injection, the number of abdominal contractions in each mouse was counted over a 30-minute period. A significant reduction in writhing compared to the control group was considered a positive analgesic response. The percentage of inhibition was calculated following formula where nC represents the average number of contractions in the control group and nt represents the average number of contractions in the treated group:

$$\%\ Inhibition/protection = \frac{nC-nt}{nC}\ x100$$

$$\%\ Potency = \frac{\%\ protection\ of\ the\ tested\ compound}{\%\ protection\ of\ ibuprofen}\ x\ 100$$

At the end of the experiment, all mice were anesthetized using a standardized protocol involving ketamine and xylazine. Blood samples were collected via retro-orbital puncture, after which the animals

were humanely euthanized through cervical dislocation. The collected blood samples were immediately centrifuged, and the serum was separated for the determination of prostaglandin E2 (PGE2) levels. PGE2 concentrations were quantified using commercially available ELISA kits, following the manufacturer's instructions. Absorbance was measured at 450 nm with reference wavelength of 630 nm using an ELISA plate reader (Stat Fax 2200, Awareness Technologies, Palm City, FL, USA). All reagents and chemicals used were of the highest commercially available analytical grade.

Antipyretic effect

The antipyretic activity was evaluated using four groups of rats (n=5 per group). Baseline rectal temperature was measured using a digital thermometer prior to yeast injection. Each animal was then given an intramuscular injection of Brewer's yeast (1 mL/100 g bwt of 44% yeast suspended in saline) as a pyrogenic agent. The temperature was measured 24 hours following the yeast injection to confirm fever induction. Rats were considered pyretic and selected for the experiment if their rectal temperatures increased by more than 0.3 °C. Royal jelly at two doses (100 and 200 mg/kg) and the reference drug (paracetamol 150 mg/kg) or saline (control) were administered orally as a single dose,, and the rectal temperature was recorded at one, two, and three hours post-treatment [9].

Statistical study

All data are expressed as mean ± Standard error (SE). The statistical analysis employed one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test $P<0.05$ was considered statistically significant. The statistical analysis was performed using Graph-Pad Prism software (Version 7.00).

Results

Analgesic activity of royal jelly.

Central analgesic activity of royal jelly

The results revealed that only the high doses (200 mg/kg) of royal jelly showed rapid analgesic efficacy within 60 minutes of administration with pain inhibition percentages of 95.31 % at 30 minutes and 37.53% at 60 minutes, compared to the reference drug celecoxib (pain inhibition percentages of 7.98% and 21.51% respectively at the same time intervals). The reference drug failed to achieve a fast onset of action but demonstrated a slowly developing analgesic effect with a considerable long-lasting effect, demonstrating activity of over 30% at 90min and continuing with activity of over 40% at 120min.The potency was 86.2% and 92.7% for royal jelly 100 mg/kg and 200 mg/kg respectively (Table 1).

Peripheral analgesic activity of the royal jelly

The results showed that ibuprofen (200 mg/kg) as the standard drug reduced the number of writhing reflexes to 16.33 ±1.52 compared to 36.5 ±1.23 in the control group with an inhibition rate of 55.30%. Moreover, the royal jelly (100 and 200 mg/kg) reduced the number of writhing reflexes to 21.17 ±1.170 and 15.67 ±0.84 with inhibition rates of 42.01% and 57.08% respectively (Table 2 and Fig.1).

Effect of royal jelly on serum levels of PGE2

The results showed that oral administration of ibuprofen (200 mg/kg) to mice intraperitoneally injected with acetic acid significantly reduced PGE2 levels ($p \leq 0.01$) compared to the control group, with a mean value of 109 pg/mL versus 156 pg/mL in the untreated group. Similarly, oral administration of a high dose of royal jelly (200 mg/kg) resulted in a highly significant reduction in PGE2 levels ($p < 0.001$), with a mean of 97.6 pg/mL compared to the control. In contrast, the lower dose of Royal Jelly (100 mg/kg) produced only a minimal decrease in PGE2 levels, reaching 123.4 pg/mL, which was not statistically significant when compared to the control group (Fig. 2).

Antipyretic effects of royal jelly

Intramuscular injection of brewer's yeast suspension significantly elevated the rectal temperature 24 h post- administration. Oral administration of the royal jelly at two doses (100 and 200 mg/kg) showed a gradual decrease in rectal temperature induced by intramuscular injection of brewer's yeast. It was noted that oral administration of paracetamol showed rapid reduction of elevated temperature in febrile rats by 80.41% after 1 hour. However, oral administration of the high dose of royal jelly (200 mg/kg) had a delayed and long-lasting effect whereby at 2 and 3 hours, it exerted the greatest antipyretic effect (68.57% and 85.71% respectively) superior to paracetamol (62.89% and 69.07 % respectively at the same time intervals. Oral administration of the low dose of royal jelly (100 mg/kg) showed an antipyretic effect at 2 and 3 hours of 77.27% (Fig. 3, Table 3).

Discussion

Prior studies have noted the importance of royal jelly as one of the oldest bee products with high therapeutic potential, widely used to treat various diseases [10]. Pharmaceutical studies have elucidated that royal jelly has multiple activities that are attributable to their bioactive compounds, including proteins, peptides, lipids, phenolics, and flavonoid compounds [11]. The current study showed that the royal jelly had potent analgesic and antipyretic effects similar to those of standard drugs due to its antioxidant and anti-inflammatory actions.

This study found that the royal jelly had a potent analgesic effect similar to that of celecoxib, a well-established analgesic drug. This finding is consistent with that of [12] who stated that royal jellydemonstrated dose-dependent analgesic effects comparable to aspirin and morphine, particularly effective at a dosage of 200 mg/kg. Royal jelly, a nutrient-rich substance produced by worker bees, has garnered attention for its potential health benefits, including analgesic (pain-relieving) properties. This substance is known for its unique composition, including proteins, amino acids, vitamins, and fatty acids, which contribute to its therapeutic effects [13]. Royal jelly has been shown to possess anti-inflammatory effects, which can help alleviate pain associated with inflammation. By reducing inflammation, it may indirectly decrease pain levels [14]. Some studies suggest that royal jelly may influence the release of neurotransmitters involved in pain perception, such as serotonin and dopamine [15]. This modulation can lead to improved mood and reduced pain sensitivity. Additionally, the antioxidant properties of royal jelly can help protect cells from oxidative stress, which is often associated with chronic pain conditions. By reducing oxidative damage, royal jelly may contribute to pain relief [16]. The growth factors and nutrients present in royal jelly may aid in tissue repair and regeneration. This can be particularly beneficial in conditions where pain is associated with tissue damage [15]. Research has indicated that royal jelly can reduce pain response in animal models. For instance, studies have demonstrated that the administration of royal jelly led to a decrease in pain-related behaviors in rats. Royal jelly is often considered as a complementary therapy alongside conventional analgesics. Royal jelly enhances nitric oxide (NO) production, leading to vasodilation and reduced blood pressure, which may alleviate pain through improved blood flow. The vasorelaxation effect is mediated by the NO/cGMP pathway, influencing calcium channels and reducing intracellular calcium levels [17].

Notably, this study demonstrated that royal jelly decreased the levels of PGE2 in febrile rats. Remarkably, the reduction with oral administration of a high dose of royal jelly (200mg/kg) was superior to that of paracetamol. This finding is in line with results from a prior study that showed royal jelly prevented a 30% rise in prostaglandin (PGE2) [18]. Prostaglandin E2 (PGE2) is a crucial mediator in the pathophysiology of fever [19]. PGE2, which is synthesized from arachidonic acid by prostaglandin E synthases (PGES) and cyclooxygenases (COX-1 and COX-2), acts on EP receptors in the hypothalamus to raise the body's temperature. PGE2 binds to EP3 receptors on neurons in the hypothalamic median preoptic nucleus (MnPO) [20]. This binding inhibits these neurons, which triggers thermogenesis to be released and elevated body temperature. To adapt the sensitivity of the thermosensory system to accommodate elevated body temperatures, PGE2 also affects neurons in the brainstem parabrachial nucleus, which receives temperature information and transmits it to the hypothalamus[21]. Antipyretics strongly influence the production and activity of prostaglandin E2 (PGE2), a crucial mediator in the fever response Prostaglandins, such as PGE2, are synthesized from arachidonic acid by the cyclooxygenase enzymes (COX-1 and COX-2). Antipyretics reduce the body's PGE2 levels by inhibiting COX, thereby reducing the production of PGE2 which in turn reduces the signalling pathway that causes the hypothalamus to elevate the body temperature set point. As a result, fever decreases as the hypothalamus restores normal regulation of body temperature [22].

Conclusion

Royal jelly's anti-inflammatory, antioxidant, and tissue-repair mechanisms make it a promising natural treatment with analgesic and antipyretic effects. Royal jelly represents a potential adjunctive approach for pain and fever relief as with any supplement, it is crucial to consult with a healthcare professional before incorporating royal jelly into a pain management routine for fever management. Although royal jelly exhibits potential as a natural analgesic, more research is required to fully comprehend its mechanisms and optimize its therapeutic application, as its effectiveness may differ from that of synthetic analgesics.

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Declaration of Conflict of Interest

The authors declared no conflicts of interest in the publication of this research article.

Ethical of approval

All the experimental procedures and treatments were performed in accordance with the guidelines of the scientific research ethics committee, (Ethical approval No.: 444–41–46251-DS).

TABLE 1. Central analgesic efficiency of the Royal jelly.

Group	30 minute (sec)	60 minute (sec)	90 minute (sec)	120 minute (sec)	Potency%
Negative control	06.69±0.72 (--)	08.74 ± 0.65 (--)	08.70± 0.56 (--)	08.66 ± 0.38 (--)	
Celecoxib 50 mg/ kg	07.22±0.58 (07.98)	10.62 ± 0.78 (21.51)	11.46 ± 01.01 (31.72)	12.20±0.49 (40.88) *	100%
Royal jelly (100 mg/kg)	11.22±01.00 (67.80)	11.88 ± 01.16 (35.93)	11.08± 0.85 (27.36)	09.64±0.63 (11.32)	86.2%
Royal jelly (200 mg/kg)	13.06± 01.04 (95.31) *@	12.02± 0.95 (37.53)*	11.26± 0.60 (29.43)	10.68 ±0.47 (23.33)	92.7%

Data are expressed as (mean ± SE) where (n=6). Statistics were done by One-way ANOVA and confirmed by Tukey's multiple comparison tests. $p < 0.05$ was assumed to denote statistical significance. [a] statistically significant from control negative group. up. [d] Statistically significant from celecoxib group

TABLE 2. peripheral analgesic efficiency of the Royal jelly.

Group	Writhing reflexes ± SE	% Inhibition/protection	Potency%
Negative control	36.5 ±1.23	-	-
Ibu (200 mg/ kg)	16.33 ±1.52****	55.30	100
RJ (100 mg/kg)	21.17 ±1.170****	42.01	76
RJ(200 mg/kg)	15.67 ±0.84****@	57.08	103

Data are expressed as (mean ± SE) where (n=6). Statistics were done by One-way ANOVA and confirmed by Tukey's multiple comparison tests. $p < 0.05$ was assumed to denote statistical significance. * Statistically significant from control negative group. #Statistically significant from Ibuprofen group. @ Statistically significant from RJ (100 mg/kg) group.

TABLE 3. Antipyretic activity of Royal jelly in yeast-induced pyrexia in rats.

Group	Rectal Temp. (°C)							
	Normal	Basal line	After treatment					
			1hr	Inhibition %	2hrs	Inhibition %	3hrs	Inhibition %
Negative control	37.40 ± 0.42	39.25 ± 0.17	39.20 ± 0.11	-	39.20 ± 0.04	-	39.20 ± 0.42	-
Paracetamol 150 mg/kg	36.83 ± 0.77	39.25 ± 0.19	37.30 ± 0.33	80.41	37.73 ± 0.09	62.89*	37.58 ± 0.77	69.07*
Royal jelly 100mg/kg	37.85 ± 0.85	38.95 ± 0.12	38.18 ± 0.41	70.45	38.10 ± 0.04	77.27**	38.08 ± 0.85	79.55**
Royal jelly 200mg/kg	37. 78 ± 0.52	38.65 ± 0.23	38.10 ± 0.38	62.86	38.05 ± 0.19	68.57**	37.78 ± 0.52	100***

Data are expressed as (mean ± SE) where (n=6). Statistics were done by One-way ANOVA and confirmed by Tukey's multiple comparison test. $p < 0.05$ was assumed to denote statistical significance.

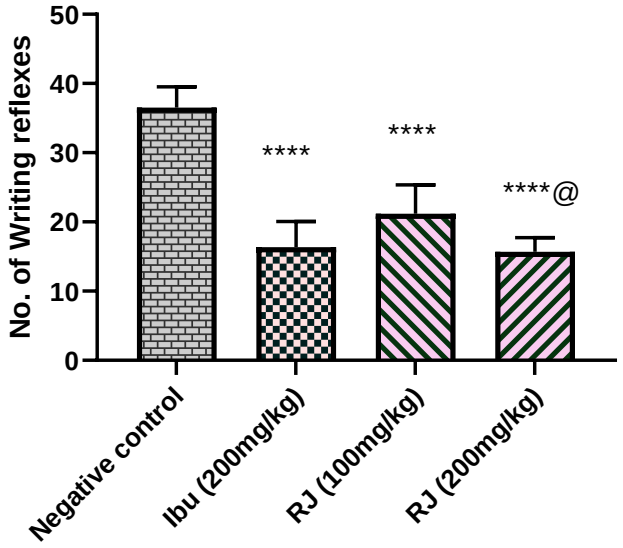

Fig. 1. peripheral analgesic efficiency of the Royal jelly showing number of writhing reflexes. * Statistically significant from control negative group. #Statistically significant from Ibuprofen group. @ Statistically significant from royal jelly (100 mg/kg) group.

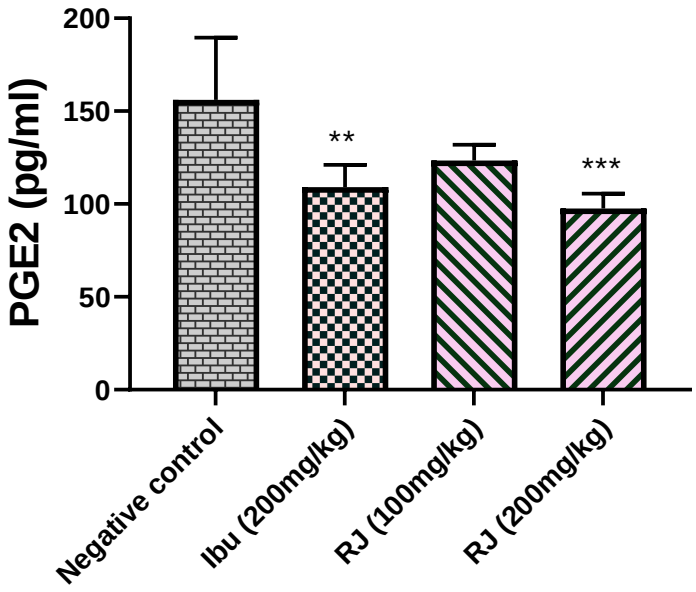

Fig. 2. Effect of Ibuprufen (200 mg/ kg) and Royal jelly (100, 200 mg/kg) compared to the control group. Data are expressed as ± SE. ** $p \leq 0.01$, *** $p \leq 0.001$.

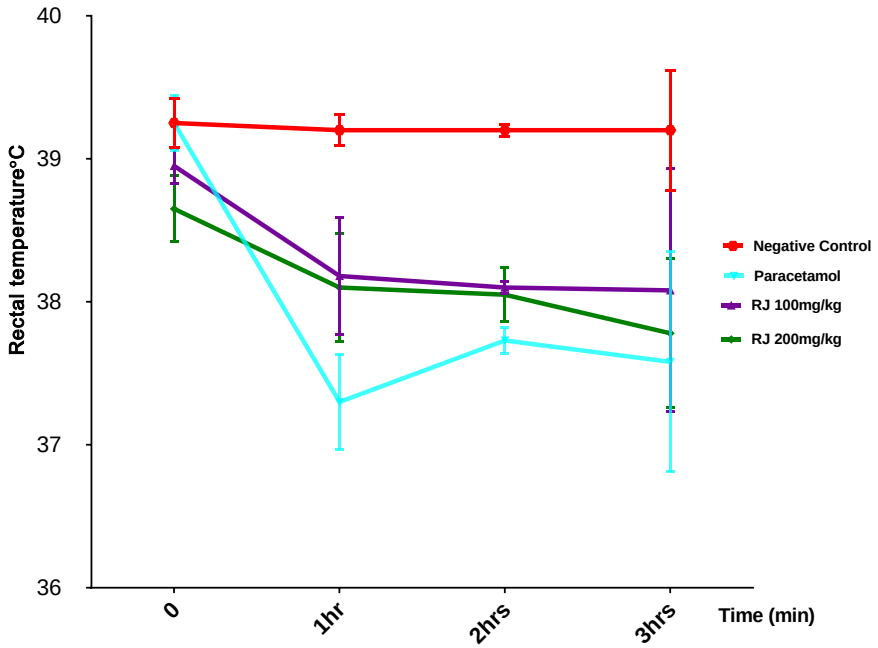

Fig. 3. Effect of oral administration of Royal Jelly (100, 200 mg/kg) on progenesis induced by intramuscular injection of rats with brewer's yeast as compared to standard drug; Paracetamol (150mg/kg). Data are expressed as (mean ± SE). Statistics were done by One-way ANOVA and confirmed by Tukey's test. $p < 0.05$ was assumed to denote statistical significance.

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غذاء ملكات النحل كمسكن طبيعي وخافض للحرارة: رؤى تجريبية من خلال تعديل مستويات البروستاجلاندين

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الملخص

البروستاجلاندين E2 (PGE2) هو وسيط رئيسي في مسارات الألم والحمى وهو ضروري لتحسس المستقبلات المؤلمة وتنظيم نقاط الضبط الحرارية في الوطاء (hypothalamus) أثناء حدوث الالتهاب. تتناول هذه الدراسة الإمكانات المسكنة والحرارية لغذاء ملكات النحل ، وهو إفراز غني بالمغذيات من النحل، في الجرذان من نوع ويستار والفئران البيضاء السويسرية، مقارنةً بتأثيراته مع الأدوية القياسية مثل الإيبوبروفين، والباراسيتامول، والسيلكوكسيب .تم تقييم النشاط المسكن باستخدام اختبار الصفيحة الساخنة للألم المركزي والتقلص الناتج عن حمض الأسيتيك للألم المحيطي. أظهرت الجرعات العالية من غذاء ملكات النحل (200 مجم/كجم) تأثيرات مسكنة كبيرة، محققةً تثبيطًا للألم بنسبة 95.31% بعد 30 دقيقة و37.53% بعد 60 دقيقة، متجاوزةً بشكل ملحوظ السيلكوكسيب. كما أظهر غذاء ملكات النحل انخفاضًا معتمدًا على الجرعة في سلوك الانقباض، مع معدلات تثبيط بلغت 42.01% لجرعة 100 مجم/كجم و57.08% لجرعة 200 مجم/كجم، مما يشير إلى تأثيرات مسكنة مركزية ومحيطية .بالنسبة للنشاط المضاد للحمى، أظهر غذاء ملكات النحل (200 مجم/كجم) انخفاضًا متأخرًا ولكنه مستمر في الحمى، محققًا 68.57% تثبيط بعد ساعتين و85.71% بعد ثلاث ساعات من العلاج. بالمقابل، قدم الباراسيتامول استجابة سريعة لخفض الحرارة (80.41% انخفاض بعد ساعة واحدة). تشير التأثيرات طويلة المفعول لـغذاء ملكات النحلإلى آلية مكملة .تسلط هذه النتائج الضوء على غذاء ملكات النحل كعامل طبيعي واعد له خصائص مسكنة ومضادة للحمى. ومن الملاحظ أن التأثير المسكن لـغذاء ملكات النحل يرتبط بانخفاض مستويات PGE2، مما يشير إلى أن آليته قد تتضمن تعديل الوسائط الالتهابية من خلال قمع تخليق البروستاجلاندين. على الرغم من أن بدايته قد تكون أبطأ من الأدوية التقليدية، إلا أن فعاليته المستدامة قد تقدم مزايا علاجية. يجب أن تستكشف الدراسات المستقبلية الفوائد التآزرية المحتملة للجمع بين غذاء ملكات النحل والأدوية المسكنة والمضادة للحمى القياسية، مما قد يستفيد من التأثيرات السريعة للأدوية الاصطناعية إلى جانب فوائد غذاء ملكات النحل طويلة الأمد لتحقيق نتائج سريرية محسنة.

الكلمات الدالة: غذاء ملكات النحل، الألم ، الحمى، مسكن، خافض للحرارة، البروستاجلاندين.