

Investigating the Impact of Varied Dosages of Royal Jelly Consumption on Creatine Kinase and Interleukin-6 Levels Post High-Intensity Resistance Training

Investigación del impacto del consumo de dosis variadas de jalea real en los niveles de creatina quinasa e interleucina-6 después del entrenamiento de resistencia de alta intensidad

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Abstract. This study aimed to investigate the effects of ingesting royal jelly sports gel at doses of 1500 mg, 3000 mg, and 4500 mg after 48 hours of high-intensity weight training on creatine kinase (CK) and interleukin-6 (IL-6) levels. A total of 16 participants were recruited and randomly assigned to four groups: placebo, 1500 mg, 3000 mg, and 4500 mg of royal jelly sports gel. Blood samples were collected before and after the intervention to measure CK and IL-6 levels. The results revealed a significant reduction in CK and IL-6 levels in the 4500 mg royal jelly group compared to the placebo group. However, no significant changes were observed in the 1500 mg and 3000 mg groups. These findings suggest that the consumption of royal jelly sports gel at a dosage of 4500 mg may positively influence recovery processes after high-intensity weight training by mitigating muscle damage and inflammation. Further research is needed to elucidate the potential benefits and optimal dosages of royal jelly in enhancing exercise recovery.

Keywords: Supplementation, Biomarkers, Royal Jelly, Fatigue

Resumen. Este estudio tuvo como objetivo investigar los efectos de la ingestión de gel deportivo de jalea real en dosis de 1500 mg, 3000 mg y 4500 mg después de 48 horas de entrenamiento con pesas de alta intensidad sobre los niveles de creatina quinasa (CK) e interleucina-6 (IL-6). Se reclutó a un total de 16 participantes y se los asignó aleatoriamente a cuatro grupos: placebo, 1500 mg, 3000 mg y 4500 mg de gel deportivo de jalea real. Se recogieron muestras de sangre antes y después de la intervención para medir los niveles de CK e IL-6. Los resultados revelaron una reducción significativa en los niveles de CK e IL-6 en el grupo de 4500 mg de jalea real en comparación con el grupo de placebo. Sin embargo, no se observaron cambios significativos en los grupos de 1500 mg y 3000 mg. Estos hallazgos sugieren que el consumo de gel deportivo de jalea real en una dosis de 4500 mg puede influir positivamente en los procesos de recuperación después del entrenamiento con pesas de alta intensidad al mitigar el daño muscular y la inflamación. Se necesitan más investigaciones para dilucidar los beneficios potenciales y las dosis óptimas de jalea real para mejorar la recuperación del ejercicio.

Palabras clave: Suplementación, Biomarcadores, Jalea Real, Fatiga

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Introduction

Throughout history, various civilizations have recognized and utilized the therapeutic properties of beehive products, including bee pollen, royal jelly (RJ), propolis, and honey (Weis et al., 2022). These bee-derived substances possess unique biochemical compositions, making them highly bioavailable and desirable for their health benefits (Botezan et al., 2023)

Vigorous physical activity has been found to potentially lead to exercise-induced muscle damage (EIMD) (Allen et al., 2018; Peake et al., 2017). The markers of EIMD comprise various manifestations, including sensations of pain, delayed onset muscle soreness (DOMS), observable swelling, restricted range of motion (ROM), diminished muscle strength and power, and compromised recovery (Hyldahl & Hubal, 2014; Ives et al., 2017). Consequently, exercise performance may also be negatively impacted (Wan et al., 2017) In practical terms, immediately after exercise, there is a notable reduction in muscle strength by approximately 20 to 50%, and it may take between 2 to 7 days for full recovery to occur (Gamonales et al., 2022; Moore et al., 2023; Peake, 2019; Peake et al., 2017). The process of EIMD is accompanied by a systemic inflammatory response that involves various mediators

(Irandoust et al., 2022; Kaniganti & Majumdar, 2019; Mukarromah et al., 2022; Philip & Fischer, 2014). Additionally, there is a release of muscle-specific creatine kinase (Bahri et al., 2022; da Silva et al., 2018; Jones et al., 2014; Tanabe et al., 2019).

The utilization of techniques aimed at mitigating exercise-induced muscle damage and inflammatory reactions resulting from intense weight training has gained considerable popularity in recent times. Among these approaches, the consumption of nutritional supplements possessing antioxidant and anti-inflammatory properties has become prevalent in addressing these concerns (Bahri et al., 2022; Faria et al., 2020; Naderi et al., 2021). In this context, royal jelly, a substance derived from bee products, is abundant in amino acids, leading to its potent antioxidant activity (Hu et al., 2021; Martinho et al., 2022; Osmond et al., 2019; Vandusseldorp et al., 2018). Royal jelly (RJ) is a nutritionally rich substance produced by juvenile worker bees through the excretion of their mandibular and hypopharyngeal glands (Anugrah, 2023). It serves as a vital nourishment for the larvae and plays a crucial role in the development of the queen honeybee (Collazo et al., 2021; Ecem Bayram et al., 2021; Jose Vazhacharickal, 2021). Moreover, RJ is recognized for its yellowish-white, creamy appearance and encompasses a distinctive blend of water,

proteins, minerals, amino acids, lipids, sugars, and vitamins (Anugrah, 2023; Zhang, Shao, Shen, et al., 2017).

The utilization of RJ supplements has demonstrated efficacy in alleviating oxidative damage and inflammation within the tissues of the central nervous system, as evidenced by findings in animal studies (Aslan & Aksoy, 2015; Chen et al., 2016; Fatmawati et al., 2019; Malkoç et al., 2018; Zhang, Shao, Geng, et al., 2017). In human studies, RJ has exhibited anti-inflammatory properties in various diseases associated with abnormal inflammation (Anugrah, 2023; Collazo et al., 2021; NAZMI et al., 2014; Tasdoğan et al., 2020). Moreover, RJ has the potential to inhibit the expression of the pro-inflammatory protein COX-2 and display antioxidant effects, leading to a reduction in NO and ROS levels in cellular environments (Malkoç et al., 2018; Ovchinnikov et al., 2022; Uçar, 2019; Yuksel & Akyol, 2016).

The potential benefits of RJ supplementation in ameliorating or attenuating EIMD and reducing circulating pro-inflammatory cytokines remain inconclusive. Presently, only one study has investigated the impact of royal jelly on markers of muscle damage and pro-inflammatory mediators. The findings of this study indicated that doses of 500 g, 1000 g, and 2000 g did not exhibit any significant effect in reducing the markers of muscle damage and pro-inflammatory mediators (NAZMI et al., 2014). Due to the limited number of previous investigations, this study aims to analyze the impact of varying doses of Royal Jelly consumption on creatine kinase (CK) and interleukin-6 (IL-6) levels after high-intensity resistance training.

Materials and Methods

Study Design

Our study utilized a pre and post-control group design, adopting a single-blind, four-arm approach. The study protocol received approval from the health research ethics committee at the Universitas Airlangga School of Medicine (Approval No. 223/EC/KEPK/FKUA/2022), and All participants who took part in this research provided written consent which generally stated their willingness to take part in the research. Before engaging in the study, participants received comprehensive instructions on research procedures and were obligated to sign written consent forms.

A total of 16 healthy young men voluntarily participated in the study and were randomly assigned to four groups. The participants in this study were selected through a random sampling technique using lottery paper to allocate them into four distinct groups. These groups included the control group, which received a placebo, the LRJ group, which was administered royal jelly at a dosage of 1500 mg, the MRJ group, which received royal jelly at a dosage of 3000 mg, and the HRJ group, which received royal jelly at a dosage of 4500 mg.

Subjects

Sixteen apparently healthy male college students (18-21 years old), voluntarily enrolled in our present study. The recruitment of participants was conducted within the confines of the local university. Inclusion criteria mandated a normal BMI and the absence of active involvement in sports training among individuals. The exclusion criteria for this research were subjects above 22 years of age, apart from that are individuals who have experienced injuries and have or are currently using any medication chronically.

Procedures

In the initial phase, we obtained the necessary ethical approvals, including feasibility permits, and secured permits to utilize facilities and infrastructure essential for the study.

Before enrolling subjects, prospective participants underwent a rigorous screening procedure based on predetermined criteria for inclusion and exclusion. Additionally, they willingly expressed their consent to participate in the research by completing an informed consent form.

The enrolled subjects were then divided into four distinct groups: the control group, which received a placebo; the LRJ group, receiving royal jelly at a dosage of 1500 mg; the MRJ group, receiving royal jelly at a dosage of 3000 mg; and the HRJ group, receiving royal jelly at a dosage of 4500 mg.

One day prior to the study commencement, the subjects were instructed to ensure sufficient rest and refrain from having breakfast in the morning. This measure aimed to standardize their physiological conditions during the exercise session.

On the initial morning of the first day, all subjects underwent data collection regarding the characteristics of the research participants. Subsequently, the subjects engaged in high-intensity weight training, specifically involving squat exercises and leg presses at an intensity level of 80-90% of their maximum capacity.

On the third day, exactly 48 hours after completing the exercises, pre-test blood samples were collected from all subjects to measure serum CK and IL-6 levels. Subsequently, the intervention was administered to each subject based on their respective assigned groups.

On the fourth day, following a 24-hour period of Royal Jelly intervention, all subjects provided post-test blood samples to assess serum CK and IL-6 levels.

In the concluding phase of this research, data analysis and report preparation are conducted, and this responsibility lies with the researcher.

Statistical analysis

Statistical analysis in this study used the IBM SPSS application, descriptive tests were carried out to obtain the mean and standard deviation. Next, the normality test is carried out using the Shapiro-Wilk method, if the data is normally distributed then a difference test is carried out

with the paired t test and independent t test, but if the data is not normally distributed then a normality test is carried out. differences were made using the Wilcoxon signed-rank test.

Results

The data of the subjects are provided in Table 1. There were no significant differences observed among the groups concerning age, body weight, height, percentage of body fat, and BMI (Table 1).

Table 1. Subject Characteristics

Characteristics	Group	Mean ± SD	Shapiro-Wilk Sig.	Kruskal Willis Asymp.Sig
Age (year)	1500 mg	20.75 ± 0.83	0.024	0.753
	3000 mg	20.75 ± 0.83	0.272	
	4500 mg	21.00 ± 0.71	0.683	
	placebo	21.00 ± 0.71	0.683	
Height (cm)	1500 mg	168.25 ± 2.28	0.369	0.808
	3000 mg	169.25 ± 2.49	0.272	
	4500 mg	167.50 ± 1.80	0.995	
	placebo	169.00 ± 2.55	0.734	
Weight (kg)	1500 mg	63.13 ± 5.79	0.997	0.876
	3000 mg	66.00 ± 5.48	0.653	
	4500 mg	64.88 ± 3.97	0.415	
	placebo	65.00 ± 2.92	0.024	
BMI (kg/cm ²)	1500 mg	22.30 ± 1.58	0.961	0.936
	3000 mg	23.00 ± 1.37	0.252	
	4500 mg	23.05 ± 1.13	0.274	
	placebo	22.78 ± 1.61	0.375	
Body Fat (%)	1500 mg	15.50 ± 1.80	0.85	0.786
	3000 mg	16.25 ± 1.48	0.85	
	4500 mg	16.50 ± 1.66	0.272	
	placebo	15.75 ± 1.92	0.103	

Note: P>0.05 = Normally distributed

The results of the normality test for Creatine Kinase levels in the research subjects who received royal jelly doses of 1500 mg, 3000 mg, 4500 mg, and placebo following high-intensity weight training are presented in Table 2.

Table 2. Results of the normality test for Creatine Kinase

Groups	Shapiro-Wilk	
	df	Sig.
Creatine Kinase Pre-test	1500mg	4 0.579
	3000mg	4 0.916
	4500mg	4 0.316
	placebo	4 0.983
Creatine Kinase Post-test	1500mg	4 0.467
	3000mg	4 0.662
	4500mg	4 0.910
	placebo	4 0.856
Creatine Kinase Delta	1500mg	4 0.571
	3000mg	4 0.288
	4500mg	4 0.375
	placebo	4 0.743

Note: P>0.05 = Normally distributed

Table 2 presents data with a normal distribution, allowing for the utilization of paired sample t-tests to evaluate significant differences between pre-test and post-test values within each group. Figure 1 illustrates the subsequent analysis, specifically the paired sample t-tests conducted to compare creatine kinase levels between the pre-test and post-test in each group. Figure 1 demonstrates that the group receiving a dosage of 4500 mg of royal jelly after high-intensity weight training experienced a significant reduction in creatine kinase levels (*p=0.012),

while the 1500 mg group (p=0.059), the 3000 mg group (p=0.055) and placebo group (p=0.091) did not show a significant reduction in creatine kinase levels.

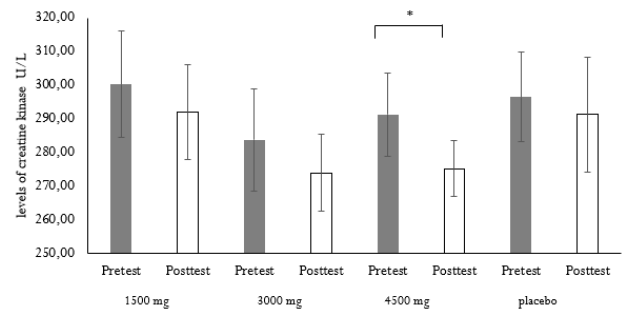


Figure 1. Paired Sample T-Test for Creatin Kinase Levels

Table 3 presents the results of the normality test for IL-6 levels in research subjects who received interventions with royal jelly doses of 1500 mg, 3000 mg, 4500 mg, and placebo after undergoing high-intensity weight training. Table 3 indicates that all data are normally distributed, allowing for the application of paired sample t-tests to examine potential significant differences between the pretest and posttest values within each group. The subsequent analysis with paired sample t-tests for IL-6 levels between the pretest and posttest in each group is depicted in Figure 2.

Table 3. Results of the normality test for Interleukin-6 (IL-6)

Groups	Shapiro-Wilk	
	df	Sig.
IL-6 Pre-test	1500mg	4 0.579
	3000mg	4 0.916
	4500mg	4 0.316
	placebo	4 0.983
IL-6 Post-test	1500mg	4 0.467
	3000mg	4 0.662
	4500mg	4 0.910
	placebo	4 0.856
IL-6 Delta	1500mg	4 0.571
	3000mg	4 0.288
	4500mg	4 0.962
	placebo	4 0.970

Note: P>0.05 = Normally distributed

Figure 2 displays the results indicating that the group administered with 4500 mg of royal jelly after high-intensity physical exercise achieved a significant reduction in IL-6 levels (*p=0.014) compared to the 1500 mg group (p=0.059), the 3000 mg group (p=0.089), and the placebo group (p=0.635).

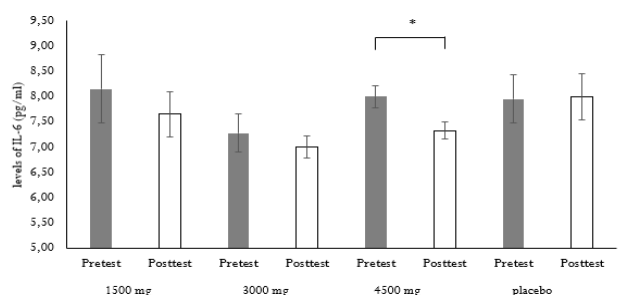


Figure 2. Paired Sample T-Test for IL-6

Discussion

Our study investigated the effect of different doses of RJ on creatine kinase (CK) levels after high-intensity weight training. This current study is believed to be the first to examine the effect of giving different doses of royal jelly after doing high-intensity weight training. The results showed that the LRJ and MRJ groups did not exhibit a significant decrease in CK levels. However, the HRJ experienced a significant reduction in CK levels following high-intensity physical exercise. Conversely, the placebo group (PLA) showed a significant increase in CK levels, which is consistent with previous research indicating that individuals without nutritional intervention experience a substantial rise in CK levels and a slower recovery process in the following 24-72 hours (De Moura et al., 2012; Jurjiu et al., 2021; Mor et al., 2021).

During weight training with eccentric movements, muscle fibers damage occurs, leading to the release of CK enzyme into the bloodstream (Fakhri et al., 2020). This process is attributed to structural changes in muscle cell membranes and protein degradation as part of the muscle adaptation process to the training load. Additionally, the increased energy demand during strenuous exercise can contribute to the elevation of CK enzyme activity (Fakhri et al., 2020; Mukarromah et al., 2022).

We found that the HRJ group demonstrated a significant reduction in creatine kinase levels. We believe this decrease is likely attributed to the amino acids present in royal jelly, which contribute to the attenuation of muscle degradation and promotion of muscle protein synthesis. Consequently, the release of creatine kinase is minimized as a result of these effects. Our findings are consistent with prior studies indicating that post-exercise amino acid supplementation enhances muscular blood flow, leading to improved oxygenation and nutrient delivery to the muscles (Harrington, 2023; Vandusseldorp et al., 2018). Additionally, amino acids play a protective role against oxidative damage in muscle cells, commonly observed during intense physical activity (Canals-Garzón et al., 2022). Consequently, this mechanism contributes to the reduction of creatine kinase levels in the blood and facilitates muscle recovery following strenuous exercise (Canals-Garzón et al., 2022; Iwasa et al., 2013; Kocot et al., 2018).

Systemic inflammation characterized by increased levels of IL-6 and accompanied by other inflammatory cytokines is triggered by high-intensity weight training (Kaniganti & Majumdar, 2019; Mukarromah et al., 2022). The presence of IL-6 following intense exercise is believed to serve a protective function against potential muscle damage associated with inflammation. Therefore, individuals who undergo high-intensity exercise may become more susceptible to infectious diseases due to increased IL-6 levels (Mukarromah et al., 2022). The PLA group demonstrated a notable elevation in IL-6 levels, consistent with previous research indicating that individuals without

nutritional intervention after weight training experience a substantial increase in IL-6 and a delayed recovery process in the subsequent 24-72 hours (Kaniganti & Majumdar, 2019; Talemi et al., 2021). Conversely, a significant decrease was observed in the HRJ group. However, the LRJ and MRJ groups in our study did not exhibit a significant decrease in IL-6 levels.

The observed decrease in IL-6 levels is attributed to the presence of specific amino acids in royal jelly, which are believed to possess inhibitory properties against IL-6 production (Ayubi et al., 2022). Furthermore, the antioxidative constituents present in royal jelly are associated with the modulation of IL-6 levels following intense physical exercise. These findings align with prior research indicating that amino acids have the capacity to impact the production of IL-6 (Tanaka et al., 2014). The mechanism underlying this process involves the regulatory impact of arginine, an amino acid compound, on the production of IL-6 by immune cells, resulting in the attenuation of the IL-6-mediated inflammatory response. Moreover, arginine exhibits immunostimulatory properties, enhancing immune system activity and influencing the immune response to infection and inflammation (Darwin et al., 2017; Martí i Líndez & Reith, 2021).

Previous studies have provided additional evidence supporting our findings, suggesting that antioxidants possess the capacity to hinder the production of interleukin-6 (IL-6) in immune cells when stimulated by inflammatory factors (Pisoschi et al., 2022). The underlying mechanism of action involves the interruption of free radical reactions and the preservation of immune cell integrity, thus mitigating the detrimental effects resulting from oxidative stress.

In the context of royal jelly, the presence of antioxidants effectively suppresses the activation of inflammatory pathways that induce IL-6 production (Askari et al., 2021; Canals-Garzón et al., 2022; Ecem Bayram et al., 2021; Silva Vasconcelos & Fernanda Salla, 2018). Effective post-exercise recovery strategies are critical for facilitating training adaptation and optimizing subsequent training sessions, particularly following high-intensity weight training. In our investigation, the Royal Jelly sourced from Tuban exhibited a notable abundance of amino acids and antioxidants (Anugrah, 2023).

The substantial presence of these amino acids and antioxidants in the royal jelly exerted a significant influence on reducing CK and IL-6 levels in the HRJ group undergoing high-intensity weight training. In contrast, in the research we conducted, the LRJ and MRJ groups did not show a significant effect on reducing CK and IL-6 levels. We speculate that the doses of 1500 mg and 3000 mg administered were insufficient to exert a notable physiological impact on the LRJ and MRJ groups. These results are strengthened by previous research which stated that RJ intake at a dose of 500-2000 mg did not have a statistically significant effect on the depreciation of markers

of pro-inflammatory mediators and muscle damage.(NAZMI et al., 2014). In addition, a greater level of protein synthesis is produced by the availability of sufficient of amino acids, so that it will have an impact on the recovery process and help maintain the ability to produce strength (Vandusseldorp et al., 2018)

There are several limitations to the research that we have conducted. Firstly, the small number of participants involved in this research has the potential to hinder achieving statistical significance, especially when conducted based on gender. Secondly, we did not assess the influence of participants' lifestyle or emotional well-being, factors that could have potentially impacted the outcomes.

This study provides evidence to suggest that swallowing pure royal jelly at a dose of up to 4500 mg after high-intensity weight training has a role in reducing CK and IL-6 levels significantly compared to doses of 1500 mg and 3000 mg. In addition, according to our study, the intake of royal jell at 4500 mg were save for humans. However, further research is needed to confirm and validate these findings.

Conclusions

According to the findings of this study, it seems that administering royal jelly at doses of 4500 mg following 24 hours of high-intensity weight training resulted in a significant reduction in serum CK and IL-6 levels compared to doses of 1500 mg and 3000 mg. Moreover, these findings indicate that royal jelly holds potential benefits in promoting recovery from eccentric exercise and may hold relevance for novice exercisers.

Conflicts of Interest

The authors declare no conflict of interest

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