Royal Jelly Potentially Reduces Oxidative Stress and Inflammation after Physical Activity: A Systematic Literarure Review

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KEYWORDS

Royal Jelly, Oxidative Stress Activity, Inflammation Action, Physical Exercise

ABSTRACT

This study aims to analyze and highlight the potential of Royal Jelly in reducing oxidative stress and inflammation after physical activity/exercise. This study used a systematic literture review (SLR) method by searching in various journal databases such as Scopus, Pubmed, ScienceDirect, and Google Scholar. The inclusion criteria in this study were articles published within the last 15 years and articles that discussed Royal Jelly, Free Radicals, and Physical Exercise. A total of 1837 articles from the Scopus, Pubmed, ScienceDirect, and Google Scholar databases were identified. A total of 13 articles that met the inclusion criteria were selected and analyzed for this SLR. For operating standards, this study followed the PRISMA assessment. The results of this systematic research review reported that the flavonoid content found in Royal Jelly has anti-oxidant properties. In addition, Royal Jelly's anti-inflammatory properties can reduce uncontrolled inflammation caused by intense physical activity and exercise. In this case, royal jelly works by inhibiting inflammation by increasing the secretion of anti-inflammatory cytokines (interleukin-10), which show significant pro-inflammatory effects such as TNF-α. We recommend royal jelly be used in individuals to reduce oxidative stress and inflammation caused by intense physical activity and exercise.

1. Introduction

Physical exercise regularly can improve health and fitness [1]. Exercise can reduce inflammatory factors and improve psychological performance by increasing serotonergic activity, modulating free radicals, and reducing inflammatory factors [2], [3]. Several publications explain that malondialdehyde (MDA) and protein carbonyls (PC) are biomarkers that indicate oxidative stress [4]. Increased ROS can lead to degenerative diseases such as cancer, cell damage, and type 1 diabetes [5], [6], [7]. In addition, highly intense exercise can cause uncontrolled oxidative stress due to an imbalance between reactive oxygen species (ROS) and antioxidants in the body [8]. Exercise at high temperatures and high intensity can cause muscle damage and energy deficiency due to metabolic stress, especially when performing eccentric movements [9]. Muscle injury from physical activity is evident from the appearance of muscle pain. Several studies have suggested that pain results from uncontrolled inflammation due to increased Tumor Necrosis Factor-alpha (TNF-a) and Interleukin 6 (IL-6) when muscles are damaged by exercise [10], [11]. Meanwhile, Creatine Kinase (CK) is considered a biomarker for muscle injury [12].

Physical exercise regularly can improve health and fitness [13]. Exercise can reduce inflammatory factors and improve psychological performance by increasing serotonergic activity, modulating free radicals, and reducing inflammatory factors [14]. Several publications explain that malondialdehyde (MDA) and protein carbonyls (PC) are biomarkers that indicate oxidative stress [15], [16]. Increased ROS can lead to degenerative diseases such as cancer, cell damage and type 1 diabetes [17].

It is necessary to find another solution to solve this issue. Royal jelly is one of the natural products produced by bees [18]. Royal jelly is a compound produced from the hypopharyngeal and mandibular glands of guard bees [19]. It has a yellow color and creamy texture, with a slightly tangy taste and aroma. Its composition consists of water (60 to 70%), protein (9 to 18%), sugars (7 to 18%) - mainly fructose, glucose and sucrose - and fat. Mineral levels in royal jelly can vary, usually ranging from 0.8 to 3.0 percent [20]. Ash and polyphenols can also be found in amounts around 0.8 to 3 percent, while vitamins are also present in small amounts. All bee larvae are fed royal jelly from the beginning of life until they become queen bees, until the end of their lives [21], [22]. Several studies have stated that royal jelly has the ability to reduce inflammation [23]. In this situation, anti-inflammatory cytokines such as interleukin 10 (IL-10) play a major role in regulating the inflammatory response [24]. In addition, royal jelly is also known for its high antioxidant content. Conversely, royal jelly has a role in inhibiting pro-oxidant activity by increasing the gene expression of heme oxygenase 1 (HO-1) and glutathione peroxidase (GPx). Royal jelly has also been utilized in the medical and health field to relieve indigestion [25].

According to analysis, royal jelly has been shown to have various functional properties such as antiseptic effects and antibacterial, anti-inflammatory, vasodilating, antihypertensive, anticancer, and antioxidant activities [26], [27]. The ability of royal jelly to be an antioxidant is caused by to the polyphenol and flavonoid compounds found in it. In addition, royal jelly also contains essential free amino acids, small peptides such as dipeptides (Lys-Tyr, Arg-Tyr, and Tyr-Tyr) obtained from the protease hydrolysis process in royal jelly proteins, peptides, proteins, fatty acids, especially 10-hydroxydecanoic acid, and vitamins [28]. Royal jelly contains major flavonoids such as quercetin, kaempherol, galangin, fisetin, pinocembrin, naringin, hesperidin, apigenin, acacetin, chrysin, and luteolin [29]. The major proteins in royal jelly (MRJP) constitutes 83-90% of the total protein content present in royal jelly and consists of nine components that have molecular weights ranging from 49 to 87 kDa [30].

In this context, the many advantages offered by royal jelly provide us with an opportunity to explore and comprehensively discuss the impact of royal jelly in reducing uncontrolled oxidative stress and inflammation after physical activity through a systematic literatur review. This study aims to analyze and highlight the potential of royal jelly in reducing inflammation and oxidative stress after physical activity/exercise.

2. Materials and Methods

2.1. Research Design

This study includes literature review research using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method. The PRISMA method is a practical guide in conducting systematic literature review research on previous research with or without meta-analysis [31]. Article searches were conducted by entering the keywords “Royal Jelly” AND “inflammation” AND “oxidative stress” AND “physical activity”.

Table 1. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Population	Humans aged 18 years and above male/female and animals (wistar rats and mice) aged 7 weeks and above.	Samples with human age below 18 years and rat or mice age below 7 weeks and physical disability and injury during physical activity.
Interventio	Studies involving physical activity,	Studies that do not involve physical

n	royal jelly induction, and Free Radicals	activity, royal jelly induction, and Free Radicals
Comparator	No specific comparisons were required in determining the inclusion criteria	No specific comparisons were required to define the exclusive criteria
Outcomes	Outcomes reported in this study related to the objectives of physical activity, royal jelly induction on oxidative stress and inflammation	The outcomes reported in this study are not related to the objectives of physical activity, royaljelly induction on oxidative stress and inflammation.
Study design	The research method is appropriate and refers to experimental research, including a control group.	Articles other than original research, such as book chapters, and abstracts from conferences.

2.2 Eligibility Criteria

Table 1 provides further information on how to determine inclusion and exclusion criteria using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) method [32].

2.3. Data Source

Databases such as Scopus, Pubmed, ScienceDirect, and Google Scholar could be used as data sources for articles published between 2009 and 2024. In addition, the keywords “Royal Jelly”, “inflammation”, “oxidative stress”, and “physical activity” were included to make the data search easier. Data were exported to Mendeley after a successful search, and then duplicates were removed.

3. Result and Discussion

Various journal databases, including Scopus, Pubmed, ScienceDirect, and Google Scholar, have been used to produce this research. Titles, summaries, and full texts of articles were screened first, then checked and stored using Mendeley software. In the first stage, 1837 articles from Scopus, Pubmed, ScienceDirect, and Google Scholar databases were found. Furthermore, in the second stage, 341 articles were screened based on the suitability of the title and abstract. In the third stage, 219 articles were verified for further processing. In the fourth stage, 84 articles were screened based on the suitability of the full article (theory, dosage, and data). Furthermore, in the final stage, 13 articles that met the inclusion criteria were selected and analyzed for this systematic literature review.

Table 2 and 3 contains brief information about the authors, sample characteristics, study design, interventions, and outcomes of the 13 articles included in the systematic literature review stage.

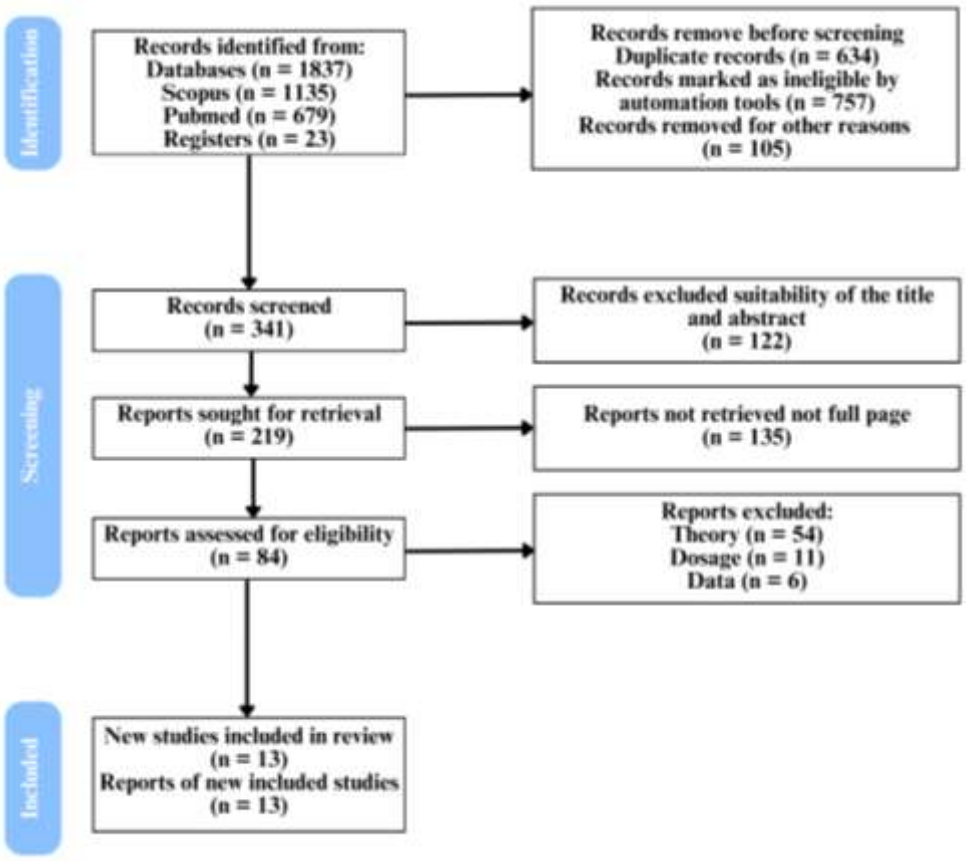

Figure 1. PRISMA flowchart for article selection process

Table 2. Results of a review of the effects of royal jelly on on animal impacts

Authors	Sample Characteristics	Study Design	Intervention	Results
Asadi at al. (2019) [33]	Twenty-one adult male Wistar albino rats (7-8 weeks old) weighing 200 ± 50 g were randomly divided into three groups. Control group (I), Varicocele and normal saline administration (II), varicocele and treatment with RJ (III).	randomized, double-blind, placebo controlled	Group III: varicocele induction and treatment with Royal Jelly (daily with 200 mg/kg) through direct gavage into the stomach	Royal jelly as antiosidant protects rats against the effects of oxidative stress varicocele. This protection may be due to the increased formation of antioxidant enzymes and the suppressive effect of lipid peroxidation and free radical formation.
Hashemi et al. (2023) [17]	We used 40 male Wistar rats that weighed between 200-250 grams. We	Placebo controlled experimental design	The rats were given RJ (150 mg/kg/day) for 14 days before they were given KA to cause TLE.	Signs of oxidative stress such as MDA, TOS, and TAC as

	split them into 4 groups: control, vehicle, KA, and RJ + KA.			well as nerve cell damage in brain sections were evaluated in all groups. Our findings showed that prior soaking in RJ chemicals significantly reduced seizure severity and made the time between first seizures longer. RJ decreased MDA and TOS and also increased TAC.
Kherideh et al. (2022) [34]	Within ten weeks, 66 eight-month-old female rats weighing 200-220 g were separated into 8 groups. The groups include a healthy control group, an experimental group with autoimmune encephalomyelitis, a sham group, and a royal jelly group with a base dose of 50mg/kg honey. All groups will be observed over a 10-week period.	Placebo controlled experimental design	The intervention was conducted daily for 5 weeks. Exercise consisted of 5 to 25 minutes of tredmill sessions at a speed of 6 meters per second, performed 5 times a week. Honey was used as the main ingredient at a dose of 100mg per kilogram of body in the exercise training group. Royal jelly with a honey concentration of 50mg/kg and exercise training + royal jelly group with a honey concentration of 100mg/kg..	Royal jelly consumed at a dose of 50 mg/kg and 100 mg/kg together with aerobic exercise has benefits on pain threshold and reducing ROS.
Shirzad et al. (2014) [35]	Sixty female mice were split into six groups of four, each containing eight-week-old mice. Take Group 1 as a baseline against which the rest of the experiment may be measured. The second group is good control. Subjects in	Placebo controlled experimental design	The sole negative control was a daily application of saline to the wounded area. Positive controls were treated with an ointment containing 2.0% nitrofurazone. The third group received 200 mg/kg of royal jelly daily, whereas the fourth group received	The results of this study reveal that daily consumption of RJ has a greater effect on wound healing than using Nitrofurazone and RJ every two days.

	Group 3 received RJ (200 mg/kg) once a day. Patients in Group 4 received RJ (200 mg/kg) twice weekly. RJ (300 mg/kg) was administered once daily to Group 5 and once every two days to Group 6.		the same amount. In the fifth group, 300 mg/kg of royal jelly was administered daily, and in the sixth group, 300 mg/kg of royal jelly was utilized daily. The findings of this study demonstrated that using RJ daily had a greater effect on wound healing than using Nitrofurazone or RJ every two days.	
Aslan et al. (2015) [36]	Five groups of 35 male Sprague-Dawley white rats weighing 300-380g each were created. Group 1, Control condition Group 2: the EG group. RJ Group is Group 3. Group 4: RJ and EG. Group 5: EG and RJ	Placebo controlled experimental design	Group 1 was given a standard meal and drinking water. The second group received normal feed and water containing 1% ethylene glycol. Group 3 was orally gavaged with 100 mg/kg of Royal Jelly. Group 4 was given water containing 1% ethyleneglycol. In addition, these rats were given 100 mg/kg of Royal Jelly daily by oral gavage. Group 5 was given 1% ethylene glycolcontaining water for the first two weeks. During the previous two weeks, mice were given 100 mg/kg of Royal	Royal Jelly's antioxidants inhibit ROS generation and assist the antioxidant system. It is believed that Royal Jelly has antiinflammatory properties through modulating signaling pathways.

Table 2. Results of a review of the effects of royal jelly on human consequences

Authors	Sample Characteristics	Study Design	Intervention	Results
Sargazi et al. (2023 [21]	80 men who were addicted to opium and undergoing methadone maintenance therapy (MMT) were randomized into four groups, including a control group	randomized, double-blind, placebo controlled	Intervention who performed resistance band exercises, Intervention who took Royal Jelly, Intervention who performed resistance band exercises and took	Total antioxidant capacity (TAC) was significantly increased in men who exercised and consumed Royal Jelly (RJ+EX) compared to the other groups.

			Royal Jelly (100 mg/kg) for 8 weeks.	
Kheirdeh et al. (2023) [19]	63 female Sprague-Dawley rats with an age range of 8-10 weeks and a weight range of 200-220 g were provided by the Laboratory Animal Breeding and Reproduction Center. Sprague-Dawley rats with EAE were assigned to seven groups: control (EAE), sham, 50 mg/kg Royal Jelly dose, mg/kg RJ dose, Aerobic Training, Aerobic Training + Royal Jelly 50 and AT + Royal Jelly 100.	randomized, double-blind, placebo controlled	The interventions given were treadmill running and royal jelly induction with various doses (50 mg/kg and 100 mg/kg).	Aerobic Training and Royal Jelly reduce inflammatory and autoimmunity regulation and reduce anxiety and depression. Royal Jelly combined with Aerobic Training induces an additive effect when using Royal Jelly dose 100 is more beneficial than Royal Jelly 50.
Petelin et al. (2019) [37]	A total of 72 participants who are 25 years old and overweight have been randomly divided into 2 groups, namely the control group and the treatment group. They will receive royal jelly products from bees.	Randomized experimental study with a control group	Royal jelly at a dose of 333 mg/kg and PA (Physical Activity)	royal jelly has the potential to exert positive effects on body fat levels, inflammation, oxidative stress, mood, and satiety in obese individuals.
Nazmi et al. (2011) [38]	Forty male swimmers, all between the ages of 18 and 25, were scouted. The swimmers were randomly split up into four groups of ten.	Placebo controlled experimental design	Groups 1, 2, and 3 were given doses of up to 1 gram and 500 milligrams. milligrams of royal jelly "for each group, while group 4. " received a fake treatment (corn) Sure. "starch" can be rewritten simply as "a type of food	Taking 500 mg, 1 gram, or 2 grams. "of royal jelly each day for" 30 days did not make things better. swimming ability Also, because of It has a lot of

			that gives energy. " If you need a different context, please provide more details. Except for the placebo group: a group that receives a fake treatment without any active ingredients. royal jelly: a special food that bees make for their queen, thought to have health benefits. Capsules were taken 20 to 30 times. a few minutes before breakfast Once a day for four weeks means doing something every day for a month.	amino acids. Please provide the full text you want me to simplify. The text you provided seems incomplete. Creatinine levels usually "get up".
Morita et al. (2012) [39]	A total of 61 healthy volunteers aged 42-83 years were enrolled and randomly divided into a royal jelly group (n = 31) and a control group (n = 30).	A randomized placebocontrolled, double-blind trial.	3000 mg royal jelly (RJ) or placebo in 100 ml fluid/day taken for 6 months.	The consumption of RJ for six months in humans improved erythropoiesis, glucose tolerance, and mental health.
Sarıtaş et al. (2014) [40]	Forty male swimmers, all between the ages of 18 and 25, were scouted. The swimmers were randomly split up into four groups of ten.	Placebo controlled experimental design	The first group received 2 g/day, the second group received 1 g/day, the third group received 500 mg/day, and the fourth group received a placebo. A total of 20 kilometers of swimming is completed in a four-week training period of two hours per day, five times each week.	Four weeks of royal jelly supplementation in this study had no effect. It is suggested to be effective with higher doses and for a longer period of time.

Büyükipekçi et al. (2018 [41]	30 healthy 20- to 25-yearold undergraduates were separated into two groups; the control group received corn starch, and the experimental group received honey.	Placebo controlled experimental design	The experimental group received 5 grams of royal jelly and 45 grams of honey, for a total of 50 grams, 20 to 30 minutes before breakfast for eight weeks. In the same way, 50 grams of placebo (corn starch) were administered to the control group.	In adolescents who performed maximal strength training, supplementation with royal jelly and honey had no effect on the increase in weight lifted, which was attributed to the weight training but did elicit hormonal alterations.
Meng et al. (2017) [42]	The study's 194 participants were split into three groups: placebo, low-dose pRJ, and highdose pRJ.	randomized, double-blind, placebocontrolled	The placebo group received no Royal Jelly, whereas the low-dose pRJ group received 1.2 g/day and the high-dose pRJ group received 4.8 g/day	The intervention had no obvious effect on physical appearance. These data imply that pRJ therapy may not increase muscular strength in the elderly but rather slow its progression.

This systematic literature review study aims to evaluate and highlight the possibility of royal jelly in reducing inflammation and free radicals after physical activity. Royal Jelly contains flavonoid compounds that have the ability to fight free radicals in the body. The chemical structure of Royal Jelly which has the chemical formula C10H20O3 (asam-10-hidroksi-dekanoat) and illustrated in Figure 2. Excessive increase in ROS production can damage muscle fibers and cause fatigue. Conversely, a small stimulus of a low increase in ROS formation can stimulate the production of natural antioxidants. However, if physical activity is performed at a high intensity, it may result in an imbalance between excessive ROS production and the antioxidant defense system, known as oxidative stress. Oxidative stress can be identified by examining biological clues such as measuring the level of Malondialdehyde (MDA) in the bloodstream.

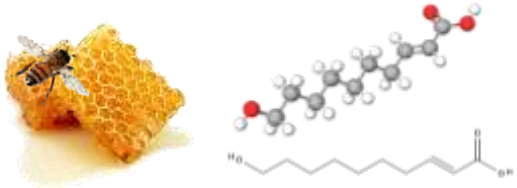

Figure 2. Chemical Structure of Royal Jelly

Research results show that royal jelly contains quite strong antioxidants. The study was conducted on 80 men and found that administering royal jelly at a dose of 100 mg/kg after resistance training three times a week for eight weeks can increase total antioxidant (TAC) levels [21]. The results of this study are supported by research on wistar rats which showed that the administration of royak with the amount of 150 mg/kg/day after being given kainic acid for 14 days can reduce the level of MDA and TOS and increase the level of TAC [17]. Furthermore, this study is supported by research showing that

administration of royal jelly at a dose of 200 mg/kg/d to 21 varicocele-induced albino rats resulted in royal jelly protecting the rats against the effects of varicocele oxidative stress [33]. From a physiological point of view, what is interesting is how flavonoids in honey can increase the concentration of mitochondrial calcium ions (Ca2+) in the cell, triggering hyperpolarization of the cell membrane [43]. Thus, an increase in Ca2+ concentration in the mitochondria could potentially reduce oxidative stress [44].

In addition, one of the most important origins of oxidative stress comes from the immune system, and inflammation is the immune system's primary response in restoring cells damaged by rigorous exercise back to normal [45]. When damage occurs to organ cells, the immune system will be activated [46]. These cells will encourage macrophages to increase their production of inflammation-inducing cytokine proteins and inflammation-fighting cytokine proteins. It is reported that TNF- alpha is one of the pro-inflammatory cytokines that increase muscle pain [18], [27], [47]. In this situation, royal jelly, which has inflammation reducing properties, can be used as an attempt to control the uncontrollable inflammatory process caused by exercise. A research study showed that administering royal jelly at doses of 50 and 100 mg/kg to 66 Wistar rats for 10 weeks after aerobic exercise on a treadmill for 5 to 25 minutes at a speed of 6 m/s five times a week can reduce oxidative stress and have an analgesic effect on pain threshold [34]. The results of a study on overweight people showed that the anti-inflammatory properties of royal jelly could significantly reduce TNF-alpha levels in the blood of mice when they experienced trigger-induced inflammation as evidenced by 72 respondents who were given 333 mg/kg of royal jelly which had a positive effect on body fat levels, inflammation, and oxidative stress due to obesity [37]. In addition, a supporting study with 63 wistar rats given royal jelly at doses of 50 and 100 mg/kg after treadmill exercise for 8-10 weeks can reduce inflammatory factors and autoimmunity regulation [19]. In a study conducted on animals, administration of royal jelly at doses of 200 mg/kg and 300 mg/kg for five consecutive days showed a greater effect on wound healing than nitrofurazone [35]. Another study found that a monthly dosage of 100 mg/kg of royal jelly reduced inflammatory indicators such as CRP and IL-6 [36]. Regarding NF-kB signaling, NF-kB is initially activated when tissue damage occurs and then plays a crucial role in regulating inflammation by promoting the release of proinflammatory cytokines such as TNF-alpha [48]. By using royal jelly to inhibit NF-kB signaling, it will also have an impact on reducing pro-inflammatory cytokines and reducing muscle pain [49].

According to recent research the antioxidants found in royal jelly are Flavonoids, a type of antioxidants that are further classified into flavonoids, flavones, flavonols, and isoflavonoids [50]. The royal jelly contains 23.3 ± 0.92 GAE μg/mg total of phenolics and 1.28 ± 0.09 RE μg/mg of total flavonoid. Pinobanksin and organic acids and their esters, for example, octanoic acid, 2-hexanoic acid, their esters, dodecanoic acid, and their esters, 1,2-benzene dicarboxylic acid, and benzoic acid are the main phenolic compounds contained in royal jelly and also the main cytokines as anti-inflammatory [51]. IL-10 is an important type of cytokine that has anti-inflammatory effects and can reduce both heritable and customized immune system reactions [19]. Previous research showed that a daily dosage of 3 grams increased erythropoiesis, glucose tolerance, and mental health in participants aged 48-83 years when supplied for 6 months [39]. A further trial with teenage swimmers found that an intervention of 0.5-2 gam/day of royal jelly had no apparent effect on their performance. Therefore, it was determined in this study that a combination of a larger intervention dose and a longer intervention period was optimal [38], [40]. Immune protection against pathogens or antigens can relieve inflammation and reduce damage to tissues [8]. Some components of Royal jelly can stimulate the formation of anti-inflammatory cytokines and initiate the release of anti-inflammatory compounds from targeted cells to maintain the body's balance [52].

DNA and tissues can be safeguarded from damage due to royal jelly. These results point to RJ's potential as a natural antioxidant, able to counteract the inflammatory response caused by UVB rays and the resulting oxidative damage. The RJ group showed that the dose of RJ had a direct correlation

with its ability to increase NRF2 levels. When a cell needs to defend itself against oxidative stress, it turns to a group of genes coordinated by the transcription factor NRF2. Antioxidant synthesis, mediated by NRF2, increases proportionally to the number of oxidants produced by cells. However, NRF2 expression is downregulated, and antioxidant synthesis is suppressed if cellular oxidant production is excessive and endogenous antioxidants are unable to compensate. Reduced levels of oxidants are one mechanism by which RJ inhibits inflammation; this decreases NF-kB expression and, in turn, TNF-alpha production [53].

The goal of this study was to find out how royal jelly influenced the performance of healthy athletes and how their bodies dealt with swelling after their muscles got hurt. Royal jelly helps lower inflammation by stopping the production of certain substances in the body that cause it, like interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-a). Studies have found that royal jelly can help ease pain, lower inflammation levels like C-reactive protein and creatine kinase, and boost exercise performance. Taking between one thousand and three thousand milligrams (mg) each day is best. This study shows that royal jelly has many benefits, especially as something that helps reduce inflammation, which is important for healing and improving performance. There haven't been any reports of bad reactions from eating royal jelly. The important thing is to find the right amount that works best to enjoy the most benefits.

Thus, royal jelly, which has antioxidant properties, can reduce the impact of oxidative stress as well as anti-inflammatory properties. Royal jelly has the ability to reduce uncontrolled inflammation caused by physical activity. Furthermore, to clarify the benefits of royal jelly in relieving oxidation stress and inflammation, please refer to Figure 3.

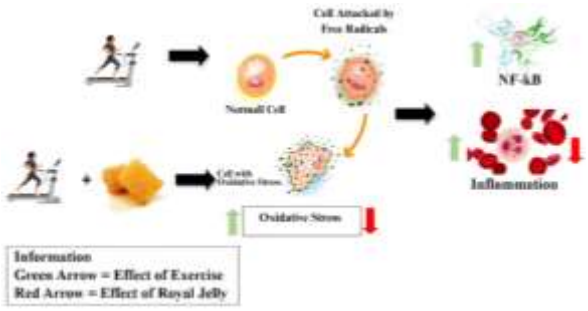

Figure 3. Mechanism of Action of Royal Jelly to Reduce Oxidative Stress and Inflammation

4. Conclusion

Royal Jelly contains flavonoids that have anti-oxidant properties that can reduce oxidative stress. In addition, the anti-inflammatory properties of bee products can reduce uncontrolled inflammation caused by physical activity/exercise. In this case, royal jelly works by inhibiting inflammation through NF-kB signaling and reducing inflammation by suppressing the secretion of pro-inflammatory cytokines such as TNF-alpha and inflammatory markers such as CRP. Reducing inflammation can reduce the intensity of muscle pain. It is recommended that royal jelly be used in individuals to reduce oxidative stress and inflammation after physical activity/exercise.

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