Chapter 24
The Potential Effect of Royal Jelly on Biomarkers Related to COVID-19 Infection and Severe Progression

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Abstract Royal jelly is a yellowish to white gel-like substance that is known as a "superfood" and consumed by queen bees. There are certain compounds in royal jelly considered to have health-promoting properties, including 10-hydroxy-2-decenoic acid and major royal jelly proteins. Royal jelly has beneficial effects on some disorders such as cardiovascular disease, dyslipidemia, multiple sclerosis, and diabetes. Antiviral, anti-inflammatory, antibacterial, antitumor, and immunomodulatory properties have been ascribed to this substance. This chapter describes the effects of royal jelly on COVID-19 disease.

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1 Introduction

Royal jelly is a yellowish-to-white jelly and creamy-like substance formed from the hypopharyngeal and mandibular glands of worker bees. It is known as a "superfood" and is consumed by queen bees [1–3]. Moreover, it is one of the most fruitful remedies for humans in both modern and traditional medicine. The properties of antiviral, anti-inflammatory, antibacterial, antitumor, and immunomodulatory have been ascribed to this substance. Other beneficial bioactive compounds reported in royal jelly include fatty acids, proteins, adenosine, acetylcholine, polyphenols, and some hormones (such as estradiol, progesterone, and testosterone) [4, 5]. Chemically, royal jelly consists of certain basic components such as water (50–60%), proteins (18%), carbohydrates (15%), lipids (3–6%), mineral salts (1.5%), and vitamins [6]. The main unique fatty acid of royal jelly is trans-10-hydroxy-2-decenoic acid (10-HDA), which has multiple biological properties [7–10]. Moreover, more than half of the proteins in royal jelly are termed the major royal jelly proteins (MRJPs), which also affect several biological pathways [11].

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One of the properties of royal jelly is due to its capability to regulate oxidative stress in the body [12]. The flavonoids and phenolic acids of royal jelly are part of phenolic class of compounds that can have an antioxidant impact [13, 14]. These confer protection of cell membranes from damage caused by over-production of free radicals [15]. Royal jelly collected 24 h after larval transfer showed the most substantial antioxidant activities. Other factors like initial larval age and time of harvest also have an impact on the antioxidant properties in royal jelly [16]. The antioxidants in royal jelly have been shown to block reactive oxygen species (ROS) production and support the antioxidant system in a rat model [17]. Also, in other animal studies, it was observed that royal jelly protected the kidneys from nephrotoxicity caused by cadmium and fluoride, most likely due to its antioxidant and anti-inflammatory effects [18, 19]. Royal jelly suppresses the production of several proinflammatory cytokines such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor α (TNF-α). Additionally, royal jelly reduces capillary permeability in the acute phase of inflammation causing a lower inflammatory response in the human body [20].

Royal jelly has various biological effects on the human body. An intervention with RJ for 3 months significantly decreased total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) levels by improving the levels of dehydroepiandrosterone sulfate (DHEA-S) [21]. Another study investigated the effect of 6 weeks of selective aerobic exercise and consumption of royal jelly on liver enzymes of multiple sclerosis patients [22]. This showed that royal jelly administration significantly reduced biomarkers of liver damage (aspartate transaminase and alanine transaminase) in these patients. Another study revealed that the administration of royal jelly may be beneficial in weight management of diabetes patients [23]. Also, royal jelly can improve erythropoiesis, glaucous control, and mental health [21]. In another study of multiple sclerosis, royal jelly administration in combination with exercise found a decrease in high-sensitivity C-reactive protein (hs-CRP), TNF- α, and neutrophils [13]. Additionally, 10-HDA can elevate the synthesis of ovulation hormones, maintaining a lower expression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in young ovarian cells [24]. Royal jelly administration also shortened the cure duration of desquamated skin lesions [25]. A randomized controlled trial recommended that intensive care unit (ICU) patients who are connected to a ventilator inhaled forms of propolis and royal jelly as use of these compounds as adjuvant therapy for COVID-19 treatment helped to reduce disease symptoms [26]. Moreover, many studies have advocated potential antiviral effects of bee products such as royal jelly, honey, propolis, and bee bread, by the direct impact of various bioactive components of these such as peroxides, flavonoids, and phenolics [27].

The key proteins in royal jelly are the MRJPs. MRJP2 and MRJP2 isoform X1 represent two functional dietary proteins present in royal jelly that through their sialidase activity and ability to interact with the angiotensin-converting enzyme 2 (ACE2) binding site of the viral spike receptor-binding domain (RBD) complex are thought to block binding of the SARS-CoV-2 virus to host cells. According to docking analysis, these MRJPs also bind to the active site or cofactor binding site residues of the SARS-CoV-2 non-structural proteins (NSP) 3, NSP5, NSP9, NSP12, and NSP16 and inhibit their activity. Moreover, these proteins may prevent viral synonyms in the lung, such as hypoxia and related pathogenesis, because of their ability to efficiently bind to most of the oxyhemoglobin and deoxyhemoglobin binding sites on the viral NSPs [28]. In addition, MRJP 3, a glycoprotein isolated from water extract of royal jelly was proposed to have immunosuppressive and anti-inflammatory impacts on T cells and peritoneal macrophages in rat models [6]. Furthermore, the antiviral impact exhibited by royal jelly can also be used as a prophylactic agent because of its favorable effect on immune tone [29]. The alkaline and water obtained from royal jelly have also been shown to be an effective scavenger against ROS [30]. From these properties, it has been proposed that royal jelly administration could be used to diminish the effects of COVID-19 infection [31].

Another effective compound in royal jelly is 3,10-dihydroxy-decanoic acid (3,10-DDA). This molecule has been demonstrated to stimulate maturation of human monocyte-derived dendritic cells (MoDCs) and polarized T cells, contributing to an antiviral immune response [32]. A study in a rat model showed production of antibodies and proliferation of immune-competent cells in animals that received royal jelly supplementation [29, 33].

Other peptides obtained from royal jelly, such as the jelleines (jelleine I–IV), can be effective in controlling co-infections in patients with COVID-19 [1]. The result of a systematic review study showed that 7% of hospitalized patients with COVID-19 had co-infections, which was reported to be twice as high in ICU-admitted patients [34], and such co-infections were found to be reduced in royal jelly–administered patients [33].

In the absence of special antiviral drugs against SARS-CoV-2, apitherapy using royal jelly and related substances may offer hope of relieving some of the risks associated with COVID-19 disease [35–37]. In this review, the effectiveness of royal jelly on biomarkers relevant to the study of COVID-19 disease are reviewed. The effects of royal jelly on various parameters that have been investigated in these different studies are summarized in Table 24.1 and Fig. 24.1.

2 Inflammatory Biomarkers

Mounting evidence during the COVID-19 crisis has shown the detrimental role of the inflammatory response associated with this viral infection, which is responsible for pulmonary complications in these patients, leading to acute respiratory distress syndrome (ARDS) and ultimately septic shock or multi-organ system failure (MOSF) [38–41]. In this inflammatory response, uncontrolled production of inflammatory cytokines is observed [39, 42]. Under these conditions, the clinical manifestations of the disease may be accompanied by a systemic increase in inflammatory mediators and cytokines, known as a "cytokine storm." This involves massive alterations in the production of interleukin 6 (IL-6), soluble IL-6 receptor, IL-1β, TNF-α, interferon gamma (IFN-γ), IL-10, IL-2, soluble IL-2 receptor, and CRP [39, 43, 44].

Table 24.1 The effects of royal jelly on various biomarkers

Parameters	effect
Oxidative stress, reactive oxygen species (ROS) production, and inflammatory response	↓
Production of proinflammatory cytokines like interleukin-6 (IL-6), IL-1, IL-1β, and IL-8, tumor necrosis factor α (TNF-α), and IL-10	↓
Liver function tests (AST, ALT, ALP, GGT, and MDA in the liver)	↓
Autoantibodies against single-stranded deoxyribonucleic acid (ssDNA), and double-stranded deoxyribonucleic acid (dsDNA)	↓
Pathological damage such as diffuse edema, bleeding, and congestion, capillary permeability	↓
Level of nitric oxide, and creatine kinase (CK-BM) levels, creatinine	↓
The curing duration of desquamated skin lesions	↓
Level of neutrophils, erythrocytes, thrombocyte, thrombosis, and Plasma fibrinogen levels, Hs-CRP, and Neutrophils	↓
Level of lipids (TC and LDL-c levels) and cholesterol in serum and liver	↓
Total antioxidant capacity and Immunomodulatory effects	↑
Pro-inflammatory cytokines including TNF-α, IL-1β and IL-8	↑
Weight management, glaucous control, and delayed formation of atheroma plaque	↑
Stimulates maturation of human monocyte-derived dendritic cells (MoDCs)	↑
Levels of DHEA-S, erythropoiesis, level of lymphocytes, platelets, serum uric acid levels and blood urea nitrogen	↑
Anti-stress and neuroprotective effects, and mental health, and the state of memory and cognitive functions (by improving oxygenation of brain tissue), improves learning processes and spatial memory, and antidepressant activity	↑

Abbreviations: *ROS* reactive oxygen species, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor α, *ssDNA* single-stranded deoxyribonucleic acid, *dsDNA* double-stranded deoxyribonucleic acid, *CK-BM* creatine kinase, *MoDCs* maturation of human monocyte-derived dendritic cells, *IFN-γ* interferon gamma, *sIL-2R* soluble interleukin 2 receptor, *CRP* C-reactive protein, *DHEA-S* dehydroepiandrosterone sulfate, *ALT* alanine transaminase, *AST* aspartate transaminase, *ALP* alkaline phosphatase, *MDA* malondialdehyde, and *GGT* gamma-glutamyl transferase

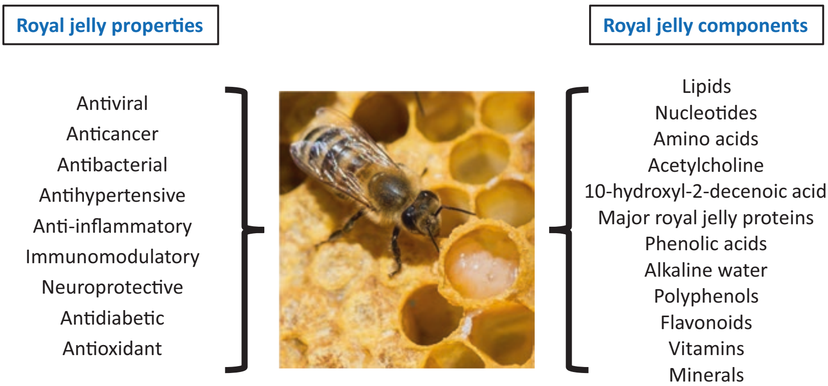

Fig. 24.1 Royal jelly properties and components

In this respect, the presence of 10-HDA in royal jelly can confer an anti-inflammatory effect [45] and inhibit the over-production of pro-inflammatory cytokines by activated macrophages [46]. This has been demonstrated in animal models, which showed that the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-8 was inhibited by 10-HAD [47]. In addition, administration of royal jelly to mice has shown a significant decrease in IL-10 serum levels, as well as the circulating levels of autoantibodies against single-stranded deoxyribonucleic acid (ssDNA) and double-stranded deoxyribonucleic acid (dsDNA) [48].

3 Hematological Biomarkers

In the first 2 weeks of contracting COVID-19, the number of leukocytes and lymphocytes in the peripheral blood can be normal or slightly reduced [49]. However, elevated neutrophil/lymphocyte and platelet/lymphocyte ratios can be indicative as biomarkers for risk of a more serious disease course [43, 49]. Complete blood counts (CBCs) are inexpensive and easy to evaluate in this regard, including the composition of white blood cell, lymphocyte, and platelets, as well as mean platelet volume. This routine test provides useful information to the physician and plays an important role in the early diagnosis of diseases such as pneumonia [50, 51]. Neutrophil white blood cells and lymphocytes are among the most indicative parameters that indicate primary inflammation [52]. An increase in the ratio of neutrophils to lymphocytes is an important indicator that inflammation is in progress [50]. In animal models, royal jelly administration has been shown to drive normalization in the neutrophil to lymphocyte ratio, stimulate the production of antibodies, and enhance the immune response [29]. It also reduces the level of erythrocytes and self-reactive B lymphocytes in the spleen [48].

4 Coagulation Biomarkers

Coagulation disorders have been reported relatively frequently in patients with COVID-19, especially in severe cases [53, 54]. Many studies in the field of COVID-19 have shown that the prothrombin time (PT; a measure of clotting time), D-dimer, and fibrinogen are increased in severe cases of COVID-19 [55–57]. The cytokine storm caused by COVID-19 infection appears to lead to development of vascular thrombi [58]. In COVID-19, the number of platelets is usually normal with a small amount of thrombocytopenia [59, 60]. However, high thrombocytopenia has been reported in severe cases of this disease [61]. Khazaei et al. [62] showed that the administration of royal jelly to rats that had thrombocytopenia improved platelet levels. Royal jelly reduces plasma fibrinogen levels in animal samples. Also, the occurrence of thrombosis in mice treated with royal jelly was less than in untreated control mice [63].

5 Renal Biomarkers

Most COVID-19 patients who experience acute kidney disease (AKI) have proteinuria and hematuria, and in severe cases, they may have acute tubular necrosis and need dialysis [64]. Possible mechanisms in the pathophysiology of AKI related to COVID-19 include direct viral entry into kidney cells, unbalanced activation of the renin-angiotensin system, or damage caused by the cytokine storm, thrombotic status, or non-specific mechanisms, such as heart failure, hypovolemia, hospital sepsis, and nephrotoxicity [65]. Supplementation with royal jelly has been shown to reduce nephrotoxicity, serum uric acid levels, and blood urea nitrogen [66]. A case series on patients with chronic kidney diseases showed royal jelly can also lead to a reduction in the circulating levels of creatinine, a widely used biomarker of kidney function [67].

6 Cardiac Biomarkers

An increased incidence of cardiovascular diseases (CVDs) has been found in patients with COVID-19, especially among those with more severe disease [68–71]. Results from a meta-analysis by Sheth et al. [72] showed that troponin, lactate dehydrogenase (LDH), and brain natriuretic peptide (BNP) levels were higher among patients with COVID-19 who died or were severe ill compared to non-critically ill patients who survived. This study also showed that there was a significant difference in D-dimer levels in patients who were dead or critically ill. Additionally, creatinine kinase (CK) levels were significantly higher only in those who died compared to those who were alive. However, there was no significant difference in CK levels between patients with severe COVID-19 compared to non-severe controls. Another meta-analysis study showed that increased levels of cardiac biomarkers including troponin I, cardiac troponin T, high-sensitivity cardiac troponin, high-sensitivity cardiac troponin I, high-sensitivity cardiac troponin T, creatine kinase-MB, and myoglobin were associated with severity of COVID-19 disease and with an increased risk of mortality [26]. Administration of royal jelly was shown to reduce the levels of malondialdehyde, nitric oxide, and creatine kinase (CK-BM) levels, and this supplementation also ameliorated pathological damage such as diffuse edema, bleeding, and congestion [73]. A meta-analysis by Vittek et al. [74] demonstrated that consumption of royal jelly by experimental animals significantly reduced the levels of lipids and cholesterol in serum and liver and delayed the formation of atheroma plaque in the aorta even in animals that had been fed a high-fat diet.

7 Liver Biomarkers

In addition to respiratory complications, the COVID-19 crisis was also associated with liver dysfunction and damage [75]. In a study in Wuhan, China, it was seen that about half of the examined patients had abnormally increased levels of biomarkers of liver damage [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] [59]. In a study by Cia et al., [76] more than 70% of patients with COVID-19 showed abnormal levels of these liver enzymes and more than 20% experienced liver damage. In another study, about 40% of patients on admission with COVID-19 had abnormal liver function tests, such as increased ALT, AST, alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and total bilirubin [77]. In an experimental study, long-term administration of royal jelly significantly reduced the levels of ALT, AST, ALP, GGT, and malondialdehyde (MDA) in the liver, with a protective role against liver lesions. Additionally, royal jelly has been found to enhance total antioxidant capacity, as a mechanism of preventing liver damage [78, 79].

8 Brain Biomarkers

It has been emerging for more than a year now that neurological damage can occur in some COVID-19 patients, consistent with the ability of the SARS-CoV-2 virus to infect the central nervous system (CNS) [80, 81]. In addition, many patients who have recovered from COVID-19 can experience depression, anxiety, and memory loss [82, 83]. Administration of royal jelly was found to improve some of these adverse neurological effects in an albino rat model by reducing oxidative stress levels in brain tissue [84]. Also, results from a randomized clinical trial showed that supplementation with royal jelly had beneficial effects on the level of consciousness in brain trauma injury patients [85]. At least one aspect of the mechanism of these effects appeared to involve enhancement of oxygenation in the brain tissue [86]. Furthermore, royal jelly has shown to have anti-stress and neuroprotective effects under stressful conditions [87]. In addition, 10-HDA has been shown to have anti-depressant activity and improve learning and spatial memory in animal models [88, 89].

9 Conclusion

Royal jelly as a superfood has been shown to have many beneficial effects on COVID-19 disease sequelae, including strengthening of the immune system, as well as antiviral, antibacterial, and antifungal impacts (Fig. 24.1). This can result in protective effects against damage that can occur to organs and tissues as byproducts of viral infection. Thus, further preclinical and clinical studies should be conducted using relevant molecular and physiological biomarker readouts to investigate the effects of royal jelly and its components during the continuation of the current pandemic and in preparation for the next one. Such treatments may help to alleviate the damaging effects of new viral outbreaks while awaiting development and deployment of effective vaccines.

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Competing Interests The authors declare no competing interests.

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