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Mini-review

Biological activities of royal jelly: a mini-review

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Abstract

Royal jelly is a bee product made by the cephalic glands of nurse bees that have been utilized in medicine for ages because of its unique therapeutic properties. Proteins, royalisin, jelleins, fatty acids, and 10-hydroxy-2-decenoic acid are among the bioactive components found in royal jelly. There are many studies vouch that royal jelly has antioxidant, antimicrobial, anticancer, fertilization, wound-healing, anti-aging, insulin-like, antimutagenic, antidiabetic, and anti-inflammatory potentials. The bioactive components it contains are primarily responsible for these functions. This study is aimed to review the biological activities of royal jelly.

Keywords: Royal jelly, Biological activity, Honey bee, Nurse bee

1. Introduction

Royal jelly (RJ) is a nutrient that is produced by the hypopharyngeal and mandibular glands of worker honeybees and it has a critical part in the development of the queen bee and larvae [1]. It is a yellowish-white color secretion product and has an acidic, creamy characterization with a sharp odor and taste [2].
Proteins, peptides, carbohydrates, fatty acids, and other bioactive compounds abound in RJ. Its variability is mostly determined by the flora's richness, which is unique to each geographic location, as well as the feeding season [3]. It has highly functional and nutritive properties due to the presence of numerous amounts of free amino acids, lipids, vitamins, and sugar [4]. The primary bioactive components of RJ are known as proteins, peptides, royalisin [5], fatty acids, trans-10-hydroxy-2-decenoic acid (10-HDA) [6]. Only RJ has been discovered to include 10-HDA, the fatty acid that is assumed to be the most prevalent in RJ [7]. As a result, 10-HDA has an immun-modulatory effect [8], and could be used to differentiate RJ from other honeybee products [9].
RJ has been researched extensively over the last 20 years, and numerous proteins have been discovered as playing a key part in the biological process. The primary RJ protein family or apalbumins plays a vital function in feeding the queen bee. Furthermore, the synthesis of honeybee products as well as the distinction of the queen from worker bees, appear to be important effects of apalbumins [10]. Major components of RJ are the proteins that compose more than 50% of its dry weight and there are 9 members of the major RJ proteins (MRJPs) family: MRJP1-9 account up more than half of the dry weight of RJs and 80 percent to 90 percent of the total protein content [11]. MRJP1 has been widely investigated and it has been demonstrated to exhibit a number of biological functions that might be beneficial in a variety of therapies [12].
RJ has an acidic property with a pH range of 3.6 to 4.2, however, some researchers have extended this to 3.4 to 4.5 [13]. Water makes up the majority of the composition (50–70%), followed by proteins (9–18%), carbs (7–18%), lipids (3–8%), trace minerals (0.8–3%), vitamins, phenols, and amino acids [14]. Sugars have a chemical makeup comparable to honey, consisting mostly of fructose and glucose. According to the first reports, the worldwide proportion of the glycid component in RJ ranged from 7.5 to 15% [15]. In general, the total amount of fructose and glucose in RJ amounts to 90% of the total sugars. The percentage of sucrose in each sample varies greatly. Additional sugars found in considerably lower amounts include maltose, trehalose, melibiose, ribose, and erlose [16].
RJ one of the valued products of bees has been used in traditional medicine and most countries offer RJ as medication, food and cosmetics, especially in China and Japan [17]. In many countries, RJ possesses many functional pharmacological potentials including antioxidant, neurotrophic, hipoglicemiant, anti-hypercholesterolemic activity and hepatoprotective, antitumor, anti-bacterial, anti-inflammatory, immunomodulatory, and anti-allergic, general tonic, antiaging, etc. [18]. Furthermore, RJ has wound-

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healing activity [19], insulin-like activity [20], and collagen production promoting activity [21]. The interest in RJ research has grown in the last two decades and new data has emerged regarding its mechanisms of action that support some of its therapeutic and medicinal applications. The purpose of this article is to provide a brief review of the biological activities of RJ.

2. Potential Biological Activities of Royal Jelly

Laboratory animals, microorganisms, agricultural animals, and clinical trials are used to explore the biological activities and usage areas of RJ (Figure 1) and its use *in vivo* and *in vitro* experimental models. The biological activities of RJ vary and have been linked to the active component concentration [22,23].

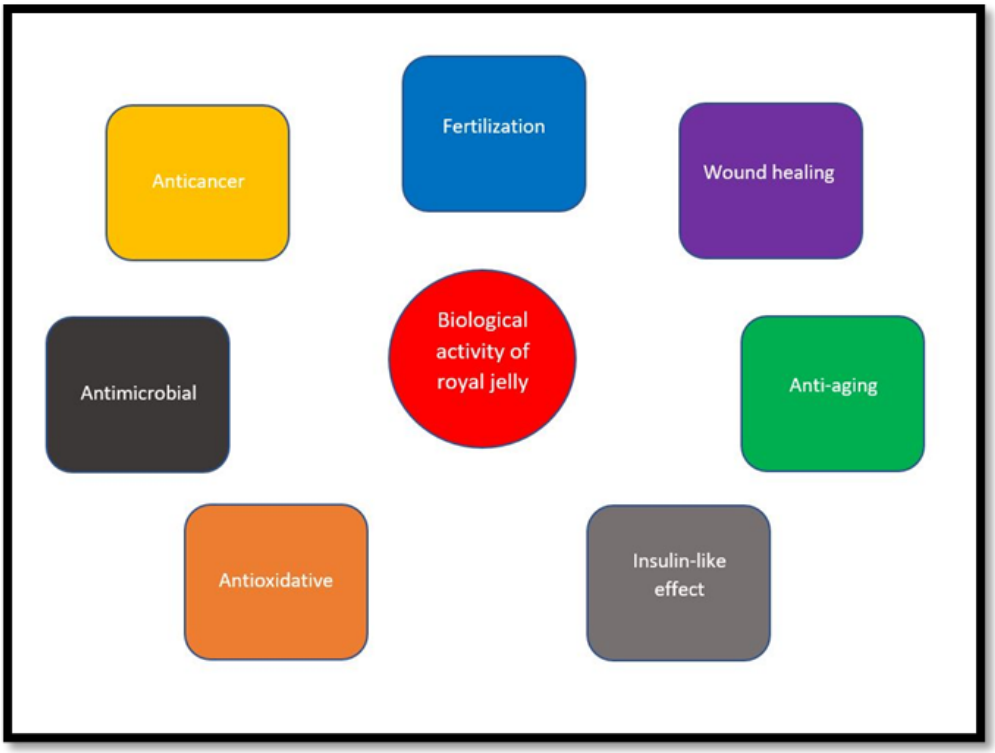

Figure 1. Biological properties and medicinal uses of RJ and its bioactive components.

3. Biological Activities of Royal Jelly

3.1. Antioxidant Activity

The release of reactive oxygen species (ROS) in organisms causes oxidative stress, which is linked to several disease processes. The various advantages of particular substances' antioxidant activity against different diseases have been established in several studies. It was discovered around the turn of the century that RJ had antioxidant properties. Furthermore, its proteins (MRJP 1–9) and peptides were identified to be responsible for this action. Since then, several research has been conducted to see if RJ's antioxidant capability might aid in medical purposes [14]. In another study, 29 peptides with antioxidant activities were derived from RJ and these small peptides with 2-4 amino acid residues have been shown to have antioxidant activity. The majority of these peptides include tyrosine residues at their C-termini, which enable them to scavenge hydroxyl radicals and H_2O_2 [24]. Antioxidant properties of enzymatic hydrolysates, water, and alkaline extracts of RJ have recently been investigated [25]. RJ's antioxidant effect has been proven *in vitro* on plants, yeast, rats, and laboratory animals. In rat and *in vitro* experiments, lipid peroxidation was also decreased [23]. RJ treatment decreased oxidative stress in diabetes patients' erythrocytes by improving malondialdehyde (MDA) levels and glutathione peroxidase and superoxide dismutase activity, according to clinical investigations [27]. A study reported that RJ significantly reduced oxidative stresses induced by fumonisin and dramatically improved antioxidant capacity [28]. RJ has been discovered to protect DNA from oxidative damage in tissues. Researchers observed that after feeding RJ to mice for a while, the levels of an oxidative stress marker in DNA and blood were considerably decreased, and the average life span of mice was enhanced due to the reduced oxidative damage [29]. RJ

was shown to have a considerable protective role against cadmium-induced oxidative damage and genotoxicity by inhibiting MDA synthesis and increasing decreased glutathione [30]. In another recent study, RJ has been shown to stimulate antioxidant activity and regulate the gut flora [31,32]. RJ's antioxidant activity could be studied as a treatment or preventative for a number of chronic and degenerative diseases [22].

3.2. Antimicrobial Activity

and

RJ has been used as a powerful antimicrobial agent since antiquity. Many studies have claimed that 10-HDA, the most significant fatty acid of RJ, has significant antibacterial effects against various infections [10,22]. Antibiotic activity of 10-hydroxy-2-decenoic acid has been observed against a variety of bacteria (*S. pyogenes, E. coli, S.aureus, S. griseus*, and three unclassified strains of Streptomyces) [10,23]. RJ components that are hydrosoluble, such as proteins and peptides, have a strong ability to inhibit Gram-positive bacteria. All of these antibacterial components are thought to have a role in the protective immune system of bees [23]. RJ is also effective on fungus. Moselhy et al. (2013) found that RJ has antifungal properties toward *A. fumigatus, A. niger, C. albicans*, and *S. racemosum* [33]. The ether-soluble fraction of RJ, on the other hand, is efficient against bacteria like *S. aureus, E. coli*, *S. griseus*, and three unidentified Streptomyces strains [34]. A comparison of the antibacterial ability of fatty acids (mostly including 10-HDA) dissolved in ether, and ether-insoluble fractions, which included Royalisin, was also carried out. These fractions were tested for antibacterial features against a variety of pathogens (some strains of *Streptomyces* species*, S. aureus*, and *E. coli*). The findings of this investigation demonstrated that ether-soluble fractions of RJ significantly inhibited the development of the previously characterized bacteria, but non-soluble fractions had virtually minimal antimicrobial activity [35]. In a recent study, when RJ was administrated to *C. elegans*, the worms have been shown to have a longer survival time against bacterial infections versus the untreated group [36].

3.3. Anticancer activity

RJ has anti-cancer characteristics such as the suppression of tumorigenesis in the liver/lung, as well as the stimulation of immune function, by inhibiting tumor-induced angiogenesis [22]. RJ inhibits cell proliferation and enhances apoptosis in different types of tumor cells, as well as affecting the production of different chemokines, antioxidants, and growth factors, and the expression of cancer-related molecules in people with cancer, particularly those treated with anticancer medications, according to *in vitro* and animal studies. As a result, RJ is considered to inhibit tumor development and protect against drug-induced side effects. RJ has also shown to be effective in the treatment of cancer for reducing side effects, maintaining the quality of life throughout treatment, and improving prognosis [37]. The preventive therapeutic approach of RJ therapy was shown to minimize the formation of breast cancers in mice while concurrently improving the antioxidant capacity of the serum, liver, and kidney. The effectiveness of RJ supplementation in diets was confirmed by various researchers. According to their results, the antioxidant and immunomodulatory properties of RJ are crucial in antitumor growth [38]. RJ was discovered to have antienvironmental estrogen activity in a study. Bisphenol-A is a kind of estrogen found in the environment that promotes the growth of human breast cancer MCF-7 cells. RJ reduced the growth-promoting impact of Bisphenol-A on MCF-7 cells, although having no effect on cell proliferation in the absence of BPA, according to the researchers [39]. In a mouse model of breast cancer, RJ has been given orally reduced tumor growth significantly as a prophylactic-therapeutic approach; however, no similar anti-cancer efficacy was identified when given after tumor cell injection [38]. RJ has a powerful anti-proliferative effect, inhibiting the growth of SH- SY5Y neuroblastoma cell lines [40]. RJ not only reduced the development of 4T1 breast cancer cells but also enhanced the immunity of breast cancer-induced animal models, as seen by elevated TNF- and decreased IL-6 and IL-10 levels [41]. The effect of RJ on the proliferation of WEHI-164 fibrosarcoma cells in syngenic Balb/c mice was investigated in a study. Different doses of RJ demonstrated efficacy against WEHI164 fibroblastoma in BAlb/c mice. The findings revealed that RJ has a significant function in fibrosarcoma cell control and regression [42]. A recent study was carried out to show cancer cell inhibition activity by RJ toward cervical (HeLa), colon and normal cell lines. The results revealed that RJ inhibits the HeLa cell line more effectively than the WiDr cell line [43].

3.4. Effect on Fertility

RJ has recently been shown to have beneficial effects on male fertility in a variety of species [44,45,46]. Infertile males who get RJ had higher sperm motility and higher male hormones such as luteinizing hormone, and testosterone. Long-term RJ feeding enhances testosterone and sperm production in male hamsters by halting the age-related decline in reproductive activity [22]. RJ has been proved to eliminate harmful effects on the male reproductive tract [39]. A study showed that RJ increased sperm motility, morphology, and increased testosterone levels [47]. Various methods have been used to examine the possible estrogenic action of RJ [48]. Changes in proteolytic enzymes, cytokines, prostaglandins, and nitric oxide levels have been shown to cause an increase in reactive oxygen species (ROS), increasing

ovarian blood flow and aiding follicular rupture during the last stages of oocyte maturation [49]. Furthermore, an excessive amount of reactive oxygen species, which can potentially cause oocyte injury, can disrupt the antioxidant defense mechanism and cause oocyte damage [50]. Multiple pathological processes, especially in the ovary and uterus, are aided by abnormal ROS levels, resulting in reduced pregnancy hormones and luteal regression. The presence of antioxidant activity of RJ has been extensively studied and proven in the male reproductive system. However, there is not much data about the effect of RJ on the reproductive system of juvenile females [51]. According to a study of 99 couples with asthenospermia causing infertility, the treatment of this condition was found simply and effectively with intravaginal administration of RJ and honey [52]. RJ has been shown to increase fertility in women who use it on a regular basis for at least six months. On the other hand, it has been proven that RJ includes stimulating components in the reproductive system development of especially female mice [53].

3.5. Wound Healing Activity

Since antiquity, RJ has been reported as being used in traditional medicine to aid wound healing [54]. Wound-healing properties of RJ make it an excellent ingredient in cosmetics and skincare products. There are limited research publications on RJ's anti-inflammatory effects [55]. RJ, a traditional cure for a variety of cutaneous ailments, might be useful in the treatment of atypical wounds. Previous research has shown that RJ or its components promote wound healing in both animals and cells. The manufacturing and use of specific RJ in wound healing, as well as the characterization of biologically active components in RJ for usage in a variety of skin damage scenarios, were all proved in a recent study [56]. RJ at a dosage of 5 mg/mL stimulates fibroblast migration in humans by changing the levels of various lipids and increasing the levels of sphingolipids that aid wound healing [57]. In an *in vitro* research, RJ showed an increased collagen synthesis in skin fibroblasts in the presence of ascorbic acid-2-O-glucoside (AA-2G), with 10-hydroxy-2-decenoic acid (10H2DA) and 10HDA. TGF-β1, a transforming growth factor crucial for collagen synthesis, was produced in response to 10H2DA [21]. Another study demonstrated that RJ promotes wound healing in diabetic leg ulcer patients, according to clinical research, and it's even more effective when combined with other conventional therapies [58]. Topical administration of RJ had a dose-dependent healing activity in hamsters with oral mucositis caused by chemotherapy [59]. The anti-wrinkle properties of Korean freeze-dried RJ and its primary component, 10-HDA, were investigated. The findings showed that Korean RJ could be effective as a significant functional health food component to improve skin health [60]. In a recent study showed that oral mucositis can be effectively treated with RJ. Their remarkable wound healing and anti-inflammatory properties might be explained by the RJ. Given that not all patients with oral mucositis have access to photo biomodulation therapy, the study also showed that topical administration of RJ might be a viable alternative to photo biomodulation therapy in the treatment of oral mucositis [61]. A recent study sheds light on RJ's wound-healing activities and investigated the components of RJ from various nectar plants [62].

3.6. Anti-Aging Activity

RJ has been used as a personal beauty secret since ancient Egypt, notably by historical figures like as Cleopatra. It is still highly significant in the cosmetic business today because of the high amount of bioactive chemicals that bestow a variety of aesthetic and health advantages, on which health experts concentrate their efforts. Despite its multiple biological characteristics, RJ is regarded as a natural anti-aging nutraceutical that promotes better body composition and fertility [63]. RJ has been linked to an increase in the longevity of queen honeybees and numerous other species, as well as an improvement in the quality of life in old-age rats. In *Caenorhabditis elegans*, RJ and ERJ treatment has the ability to postpone aging and age-related disorders, and enhance lifespan and stress tolerance [22]. The anti-epidermal growth factor receptor pathway was promoted by MRJPs, which enhanced *Drosophila melanogaster* lifespan [64]. In addition, royalactin promoted EGF and EGFR signaling pathways in *Caenorhabditis elegans* [65]. Aging is linked to a reduction in cognitive performance, and it is also the leading cause of neurodegenerative disorders [66]. RJ works as a multidomain cognitive enhancer that can recover cognitive functions in elderly and Alzheimer's Disease mice, according to preclinical results, however, the number and quality of human RJ studies in Alzheimer's disease are low [67]. Alzheimer's disease (AD) is a progressive neurological illness in which situational memory and working memory (WM) are lost [68]. The skin is impacted by estrogen level withdrawal during menopause and the normal aging process. In addition, alterations in skin collagen levels result in a loss of skin suppleness and strength [69]. In ovariectomized rats, RJ has been shown to be a preventive agent against skin aging by increasing collagen synthesis [70]. The amount of procollagen type I protein in the epidermis of estrogen-deficient female Sprague-Dawley rats increased after they were given 1% RJ. Furthermore, the amount of collagen retrieved was extremely near normal levels [71].

3.7. Insulin-like effect

Changes in lifestyles contribute to decreased physical activity and increasing obesity, making diabetes one of the world's most frequent chronic diseases [72]. RJ has

been used in Chinese and Japanese medicine to treat diabetes and maintain normal blood sugar levels. RJ uses insulin-like peptides and other substances to lower blood sugar levels. RJ can also maintain a healthy blood sugar level by contributing to the oxidation of glucose for energy, thanks to the insulinic impact of insulin-like peptides contained in it. In addition, the insulin found in RJ is extremely similar to the insulin found in mammals [73]. In a study conducted on 20 volunteers, it was discovered that after consuming RJ, the glucose levels of individuals fell by 11.9 percent. This finding suggests that RJ contains substances that affect serum glucose levels [74]. RJ was tested on animals to see if it reduced the effects of diabetes. Alloxan-induced diabetes in rats has been decreased by RJ. RJ has been demonstrated to reduce insulin resistance in fructose-drinking rats by raising blood insulin levels, which is noteworthy given the high fructose content of honey. These findings suggest that RJ could be an important dietary medication for diabetics [75].

4. Conclusions

RJ is a natural bee secretion with a lot of medical applications and it has a number of valuable medicinal characteristics that have been used since ancient times. RJ is nowadays a popular functional and therapeutic food for improving human health. For its health-beneficial characteristics, it is now mostly taken as a food product or found in supplementation and other products. RJ or its particular components have been shown to have antioxidant, anticancer, antiproliferative, antibacterial and antifungal, neuroprotective, wound healing, immunomodulatory, anti-aging and insulin-like effects.

Scientists are only now beginning to identify the numerous medical and nutritional benefits of this wonderful nutrient. Although some of its pharmacological and biological activities have been validated, scientists are only now beginning to discover the excellent advantages of this incredible natural product. The bioactive components and chemistry of RJ are still not fully known. More research and confirmation would be required to demonstrate any meaningful benefits and mechanisms of pure RJ and isolated molecules. To summarize, RJ has a wide range of properties that could be effective as a treatment or a component of combination therapy. Before RJ may be employed in present applications, some gaps must be filled, but for now, it appears to be a safe and effective superfood. More *in vitro* and animal research is required not just for diagnostic purposes, but also to gain a deeper understanding of the medicinal potential of this substance.

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