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Production and Some Bioactive Properties of Royal Jelly- A Review

Büşra BELTEKİN[1]* Nurullah DEMİR[2]

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Abstract

Royal jelly secreted by the hypopharyngeal and mandibular glands of worker bees (*Apis mellifera*) is a very essential bee product in terms of bee nutrition and bee variety. Although they have the same genetic structure at the beginning, the differences between the queen and the worker bee are due to the physiological and morphological changes that occur when the queen bees are fed with royal jelly. Being a bee product rich in bioactive components, consisting of carbohydrates, proteins, lipids, free amino acids, minerals, vitamins, phenolics, royal jelly is precious for human health as well as for bees. Royal jelly has functional features such as antioxidant and antimicrobial effect, anti-aging effect, anti-inflammatory activity. By virtue of bioactive effects, royal jelly is considered a nutraceutical and functional food and hereby its production and consumption demand is also increasingly enhances. Jenter, Nicot or Yasaeng, production by larval transfer or grafting are types of royal jelly production methods. This review intented to express some bioactive properties and production techniques of royal jelly.

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Arı Sütü Üretimi ve Bazı Biyoaktif Özellikleri - Derleme

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Öz

Arı sütü, işçi arıların *(Apis mellifera)* hipofaringeal ve mandibular bezleri tarafından salgılanan, arı beslenmesi ve arı çeşidi açısından oldukça önemli bir arı ürünüdür. Başlangıçta aynı genetik yapıya sahip olmakla birlikte ana ve işçi arı arasındaki farklılıklar, ana arıların arı sütü ile beslenmesiyle ortaya çıkan fizyolojik ve morfolojik değişimlerden kaynaklanmaktadır. Karbonhidrat, protein, lipit, serbest amino asit, mineral, vitamin, fenolikler oluşan, biyoaktif bileşen bakımından zengin bir arı ürünü olması, arı sütünü arılar kadar insan sağlığı için de değerli kılmıştır. Arı sütü, antioksidan ve antimikrobiyal etki, yaşlanma karşıtı etki, antienflamatuar aktivite gibi fonksiyonel özelliklere sahiptir. Biyoaktif etkiler göstermesi nedeniyle arı sütü, nutrasötik ve fonksiyonel bir gıda olarak kabul edilmektedir ve bu nedenle üretimi ve tüketimi de giderek artmaktadır. Larva transferi veya aşılama, Jenter, Nicot veya Yasaeng üretimi arı sütü üretim yöntemlerindendir. Bu derleme, arı sütünün bazı biyoaktif özelliklerini ve üretim tekniklerini açıklamayı amaçlamıştır.

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[1] https://orcid.org/0000-0002-5237-6099, Bingöl University, Bee and Bee Products Department, The Council of Higher Education 100/2000 PhD, Turkey, *Corressponding author, bbeltekin89@gmail.com

[2] https://orcid.org/0000-0002-922-7826, Bingöl University, Vocational School of Food, Agriculture and Livestock, Turkey, ndemir@bingol.edu.tr

Introduction

Royal jelly (RJ) is a valuable bee product that has been used for nutritional and pharmaceutical aims for centuries. According to historical records, the first use of royal jelly by humans dates back to the Ancient Greek period, and it has been stated that it was used in the immortality food offered to the Olympian Gods. The records also include the followings: Aristotle was the first to discover the function of royal jelly in the bee community and its effect on the queen bee; he had a mixture of honey and royal jelly prepared especially at school, at breakfast, in order to increase his physical strength and thinking capacity; in Ancient Egypt, Cheopatra used royal jelly as a cosmetic and it has been reported that she owes her beauty to royal jelly; that the Pharaoh usually consumed royal jelly, and RJ was a symbol of power in the same period. Additionally, it is noticed that RJ has been applied in traditional medicine since ancient times in Asia, especially in China.

Huber in Switzerland was the first scientist to use the name of 'royal jelly' (perfect food) in 1793 for royal jelly and first chemical analyzes of it were made by Langstroth in the United States in 1852, and effective analyzes were not possible until the 1940s. With the progress of apitherapy, royal jelly began to be used as a functional food in the 1960s. The countries that produce the most royal jelly in the world are Mexico, China, Japan and Korea. The biggest buyers of the produced royal jelly are primarily USA, some European countries with high per capita income (Yılmaz et al., 2017; Uçar, 2018).

RJ is also accepted as a "superfood" which is secreted from hypopharyngeal and mandibular glands of 5-15 days old worker bees (*Apis mellifera*) to feed young worker larvae and queen bees (Ahmad et al., 2020; Sorucu, 2019). Royal jelly is the only nutrient for the first period development of the larvae. Besides, it is used for feeding the young larvae and queen bee in the hive. Although there is no genetic difference between worker bees and queen bees, some of the larvae turn into worker bees and the other into queen bees. All larvae are fed with royal jelly for the first 3 days. In the following period, larvae fed with honey and pollen become worker bees, and those who continue to be fed with royal jelly become queen bees. Queen bees are fed with royal jelly for life and become adults by completing the larval process in 16 days. However, after the third day, worker bees fed with honey and pollen complete their development in 21 days. For this reason, while the queen bee fed with royal jelly can live for 3 years, worker bees fed with honey and pollen live for 5-6 weeks (Sabatini et al., 2009; Akyol and Baran, 2015). Queen bees, also differ physically, are larger and more durable than worker bees. Morphologically, the queen bee has an average of 42% larger and 60% more body weight than the worker bee. Another main differences between them are, for queen bees, sexual organs have developed for reproduction, while in worker bees, organs related to their work such as pollen baskets, strong mandibula, secretion glands have developed (Brouwers et al.,1987; Lercker et al.,1981). Since the formation, life and functions of the queen bee are associated with royal jelly, the use of this product in human nutrition has increased consciously in recent years. This review aims to explain physicochemical properties of RJ; antimicrobial, antioxidant, antidiabetic and antiaging effect of royal jelly and royal jelly production techniques.

Physicochemical properties of royal jelly

RJ is a water-soluble, viscous, gel-like substance with a density of 1.1 g/ml and a pH of 3.4-4.5. Abundant in nutrients, it has a pungent odor and fruity bitter taste (Shirzad et al., 2013; Maghsoudlou et al., 2019). Its color is white-yellowish and gets darker with storage time. The sensory properties of royal jelly are an important quality criterion. RJ not stored properly darkens in color becomes sourer in taste since affected by sunlight, humidity, heat and air very quickly (Akyol and Baran, 2015). It has been noticed that royal jelly should be stored frozen for optimum quality. The viscosity of royal jelly varies depending on its water content and age. Its viscosity increases and biologicial properties and bioactive ingredients loss when stored at room temperature or in a refrigerator at +5 ^{0}C (Uçar, 2018).

The chemical structure of royal jelly can vary significantly depending on the season, the region, the breed and feeding status of the colonies used in the production of royal jelly (Karacaoğlu et al., 2004; Şahinler and Kaftanoğlu, 2005). Water (60–70%), proteins (9–18%), carbonhydrate (7–18%) and lipids (3–8%) are main

components of RJ (Mellio and Chinou,2014). In royal jelly, the water content is a considerable quality criterion, the water activity is above 0.92, whereas it shows a significant level of microbial stability (Sabatini et al., 2009). Proteins are among the most essential components of RJ (Yeung and Argüelles, 2019). More than 80% of royal jelly proteins include soluble proteins and Major Royal Jelly Proteins (MRJP). MRJPs (MRJP1-9) containing many essential amino acids similar to ovalbumin and casein and having 9 members have a very important physiological role in the development of queen bees and larvae (Uçar, 2018). MRJP 1-9 contains among amino acids, arginine (48%), leucine (47%), isoleucine (39.3%), histidine (44.5%), lysine (51.4%), threonine (42%), tryptophan (48.3%), methionine (49.5%), valine (51.4%) and phenylalanine (47.3%) (Scarselli et al., 2005). Peptides are also one of the specific amino acid sequences in royal jelly. It contains structures similar to the C-terminus of MRJP-1, which can be identified by proteomics, such as jelleines-I, jelleines-II, jelleines-III, jelleines-IV, and jelleines. Peptides such as apidaesin, defensin, hymenoptaecin are other peptide components of RJ (Ahmad et al., 2020).

Carbohydrates such as fructose, glucose maltose, trehalose, melibiose, ribose and erlose take place in the RJ structure at a rate of 7.5-16%. It has been stated that the reduction of carbohydrates in RJ plays a role in its epigenetic effect through the activation of insulin-like growth factor 1 (IGF-1) and rapamycin mammalian target (mTOR) signaling cascades. Therefore, they promote the transformation of *Apis mellifera* larvae into queens by uptake of essential nutrients (Mohammed Ali and Kunugi, 2020).

The feature that distinguishes RJ from other bee products is its lipid and fatty acids content. Lipids are defined as 80-85% of free fatty acids. This composition also contains 4-10% phenolic compounds, 5-6% waxes, 3-4% steroids and 0.4-0.8% phospholipids. Approximately 80-90% of the fatty acids have a different structure, such as 10-hydroxy-2-decenoic acid (10-HDA), 10-hydroxydecenoic acid (10-HDDA), and sebacic acid (SEA). This fraction consists of 32% trans-10-HDA, 22% 10-HDDA, 24% gluconic acid, 5% dicarboxylic acids and some other acids (Terada et al., 2011). In addition, fatty acids such as 8-hydroxy octanoic acid (8-HOC), 3,10-dihydroxydecandioic acid (3,10-HDecDA), 9-hydroxy-2-decenoic acid (9-HDA), 1,10-decandioic acid (DecDA), 3 hydroxydecanoic acid (3-HHDA) and 2-decene-1,10-dioic acid (2-DecDA) can also be found in RJ (Isidorov et al., 2012). 10-HDA is a stable component that represents 3.5% of freeze-dried RJ, which is accepted as an international quality standard.

RJ comprise volatile compounds such as phenol, guaiacol and methyl salicylate, and trace elements such as potassium, sodium, magnesium, phosphorus, sulfur, calcium, zinc, iron and copper. It is rich in B vitamins such as thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, biotin, as well as phenolic compounds such as ferulic acid, quercetin, kaemferol, galangin and fisetin, pinocembrin, naringin and hesperidin, apigenin, acacetin and chrysin (Kurek-Górecka et al., 2020). Hormones, gonadotropins, pantothenic acid, testosterone, estradiol, progesterone and prolactin are also other biological components stated in RJ (Carvalho et al., 2011).

Bioactive properties of RJ

Royal jelly is one of the oldest and highly effective bee products widely used in apitherapy. In researches, the pharmaceutical properties of RJ have been attributed to some of its bioactive components, including proteins, peptides, lipids, phenolics and flavonoid compounds (Table 1). In recent years, RJ has indicated an increase in its potential for use against cancer, diabetic, cardiovascular and Alzheimer's disease (AD), antimicrobial, antioxidant, anti-inflammatory activity, vasodilator and hypotensive activities, disinfectant effect, antiaging, anti-hypercholesterolemic activity and antitumor effect (Uçar, 2018; Ahmad et al., 2020).

Table 1 Biological constituents in RJ and their responsible activities (Kurek-Górecka et al., 2020; Ahmad et al.,2020)

Components	Effect	Disease
defensin-1 peptid, ferulic acid	antibacterial	wounds, diabetic foot ulcers, acne
10-hydroxydecanoic acid, 3-10-dihydroxydecanoic acid, amino, gamma globulin	antiinflammatory	atopic dermatitis, wounds, hypertrophy, hyperkeratosis
10-hydroxy-trans-2-decenoic acid, 10-hydroxydecanoic acid	antiaging	wrinkles
10-hydroxydecanoic acid, 3-10-dihydroxydecanoic acid	immunomodulatory and antiallergenic	autoimmune and inflammatory diseases
MRJP-2, MRJP-4, jelleine I-III, jelleine-II (pS), and jelleine-II (pT)	antibacterial, antifungal, anti-yeast, anticancer, antioxidant	wounds, cancer

Antimicrobial effect

RJ has a wide variety of pharmacological functions in humans. Royalicin and jelleine peptides in its structure have strong antibacterial properties. Royalicin contains three intramolecular disulfide bonds between the six cysteine residues required for its antibacterial action. It was found to have strong antibacterial activity against gram-positive (*B. subtilis, Micrococcus luteus, Sarcina lutea, Lactobacillus helveticus, Paenibacillus larvae*) bacteria but not against gram-negative bacteria (*E. Coli, Serratia marcescens*) at low concentrations. Although royal jelly is very sensitive to colonization by microorganisms, it shows a significant amount of microbial stability. Although the detailed mechanism is not well known, it has been concluded that the primary antibacterial effect is due to the interaction of cell membrane-peptides. Another antibacterial protein identified in royal jelly is jellein. So far, four jellein, (jelleine I-IV) groups have been identified. Studies have demostrated that jelleine I – III show antimicrobial activities against both gram-positive (*S. aureus, S. saprophyticus and B. subtilis*) and gram-negative (*E. coli, E. cloacae, K. pneumoniae, and P. aeruginosa*) bacteria, fungi and yeast (Bachanova et al., 2002; Yeung and Argüelles, 2019; Cornara et al., 2017). In addition, in another study by Bengü et al. (2020), the antimicrobial effect of Bingöl royal jelly was investigated and it was determined Bingöl RJ has antimicrobial activity against *Salmonella typhimurium, Escherichia coli and Staphylococcus aureus.*

Antioxidant effect

The antioxidant activity of RJ has been statemented to be possible in the prevention and treatment of various chronic and degenerative diseases (El-Nekeety et al., 2007). Considering that royal jelly is produced after the pollen is digested by natural enzymes of honey bee, and all pollen phenolic compounds are also found in royal jelly, it has been concluded that the antioxidant activity of royal jelly is related to phenolic compounds, proteins and peptides (Maqsoudlou et al., 2018). In in vitro studies, the antioxidative effect of royal jelly was investigated by measuring the scavenging abilities of superoxide and DPPH (1,1-diphenyl-2-picrylhydrazil) radical and ferric reducing power. Based on the results of these studies, it was concluded that royal jelly showed high antioxidant activity (Nagai et al., 2001; Maqsoudlou et al., 2018). It has been suggested that antioxidant proteins in royal jelly are agents that suppress biological aging processes and can be used in the treatment of diseases caused by oxidative stress due to atherosclerosis, hypertension, infertility, asthma, depression, diabetes and cancers. DNA tissue of rats fed with royal jelly was protected from oxidative damage and the levels of oxidative stress marker (8-hydroxy-2-deoxyguanosine) in kidney DNA and serum were decreased. It is reported that royal jelly reduces intracellular oxidation in a dose-dependent manner. It has been stated oxidative stress and apoptosis caused by cisplatin, an important chemotherapy agent, in the kidney and liver of rats are modulated by RJ (Silici et al., 2011). It acts as a powerful free radical scavenger in the liver, preventing or ameliorating the toxic effects of drugs (Li et al., 2011). In another study, the protective effect of royal jelly on the liver was mentioned. Pourmoradian et al. (2012) reported it modulates oxidative stress and apoptosis in liver and kidneys. Another well-known pharmaceutical effect of it is that royal jelly repairs alcoholic liver damage (Galaly et al. 2014).

Antidiabetic effect

Royal jelly is also antidiabetic and helps prevent insulin resistance and hypercholesterolemia in diabetic patients (Zamami et al., 2008). Insulin-like peptides in the structure of RJ are similar to insulin in mammals (Kanbur

et al., 2009). Chromium, sulfur, vitamins B3 and insulin-like peptides in royal jelly are involved in the oxidation of glucose to obtain energy and maintain optimum blood sugar levels (Ashry and Elkady, 2014). In addition, royal jelly reduces alloxan-induced diabetes mellitus, which destroys the insulin structure (Li et al., 2011).

Antiaging effect

RJ enhances anti aging activitiy (Figure 1). It has been determined that 10-HDA increases collagen synthesis, collagen supporting factor and transforming growth factor β1 (TGF1β) production in human skin fibroblasts. It has also been reported that royal jelly protects the skin against UV rays and delays light-induced aging (Uçar, 2018). RJ acts as a sedative, normalizing sebum secretion in the treatment of skin lesions and seborrheic skin and acne-prone skin, where minor sores often occur. Due to the fact that it stimulates the metabolism in the tissues, royal jelly improves the regenerative processes of the tissues. It is used in balms, creams and lotions due to its regenerative, nutritional and healing properties. RJ affects the production of collagen, which is a critical factor in preventing skin aging. Royal jelly is highly moisturizing and affects the hydration of the stratum corneum by maintaining water retention. As a result, the skin is more elastic and better moisturized (Kurek-Górecka et al., 2020).

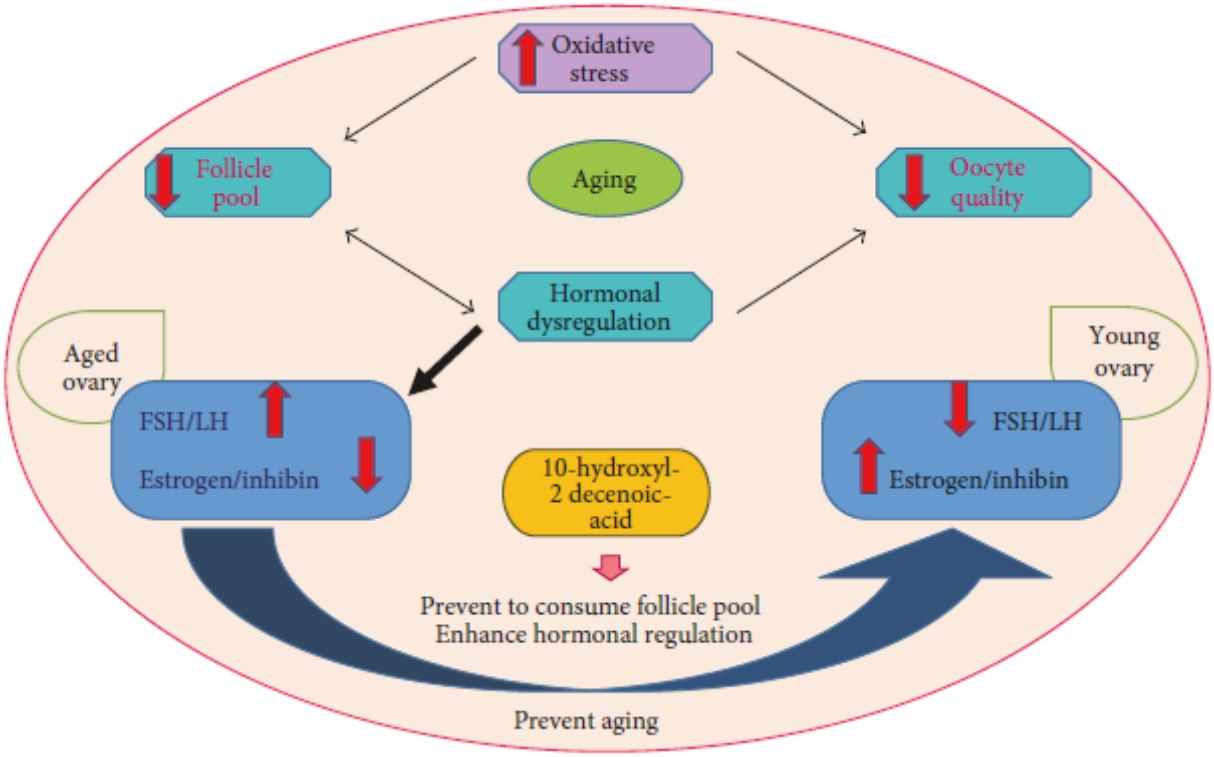

Figure 1. Molecular mechanism responsible for the antiaging activity of royal jelly (Pasupuleti et al., 2017).

Royal jelly production techniques

All proven bioactive properties of the royal jelly also triggered the development of different and efficient RJ production techniques. Natural production, Jenter, Nicot or Yasaeng, production by larval transfer or grafting (Doolitle) are examples of these techniques.

The development of techniques for the production of RJ has a long history. In 1921, Sherlock Holmes obtained this substance from a naturally produced queen cell with a syringe according to the principles of vacuum physics. In the 1950s, Mexican had begun the small-scale production and sale of royal jelly by French and Italian beekeepers (Hu et al., 2019).

In the production of royal jelly in a natural way, during routine controls between April and August, the queen cells in the honeycombs with brood (swarm) may deteriorate and be collected. The queen bee is taken from a strong hive and a comb with 1-2 eggs and 1 day old larva taken from other beehives is given to this hive every day. Thus, the production of queen cells is encouraged by the worker bees. After these processes, maximum efficiency is obtained from cells with 3-day-old queen bee larvae. The royal jelly in the cells in the honeycombs is taken with special wooden spoons. With this production technique, this process is continued for 20-30 days in a hive. Then, the queen bee is returned to this hive and the colony is restored to its former state. With the natural production technique, 20-25 g of royal jelly is obtained from a hive. Although this method is not suitable for commercial production, it can be preferred for supplying small-scale needs.

The other method is to harvest royal jelly by collecting the cells 2-3 days after the larvae transfer to the queen cells made of beeswax used in queen bee breeding (grafting). This technique is the most common royal jelly production technique known as the most suitable for mass production. Royal jelly production steps are carried out as described below.

1. Queen cell preparation

Melted wax or ready-made plastic cells are used for prepearation of queen cells. Dark colored ones should be preferred when using plastic queen cells. A wooden or silicone cell mold is used to prepare cells from melted wax. Wooden queen cell mould, pen type or group molds with a rounded end and a diameter of 9 mm and a length of 20 cm are used. The 1 cm end of the mold is made by dipping it 2-3 times into melted wax and cold water. The cells, harden in the mold and take the shape of mould, are removed from the crushing with the help of the thumb and forefinger. In order to make a queen cells in a silicone queen cell mold, melted wax is poured into the mold cavities and waited for 2-5 minutes. Then, the queen cell are taken out of the mold one by one and used (Figure 2).

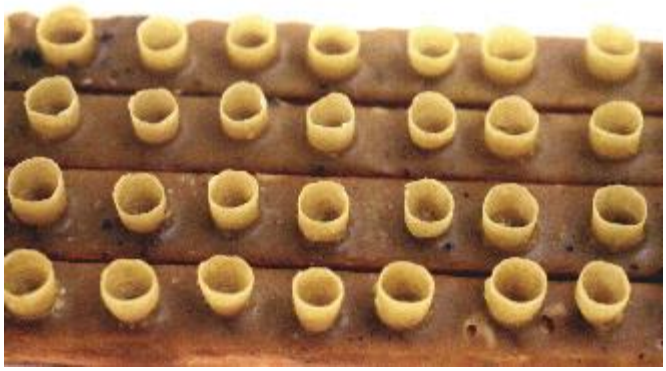

Figure 2. Queen cells (Hu et al., 2019).

2. Preparation of grafting frameworks

Prepared queen cell are adhered to 1×1.5×42 cm laths with melted wax. 15-20 queen cell are attached to each lath. By attaching 3 laths to each frame, a total of 45-60 queen cell are used (Figure 3).

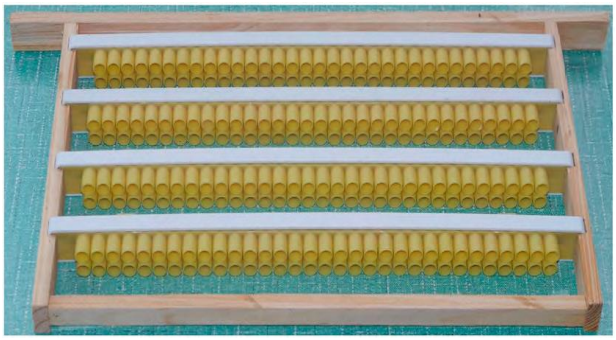

Figure 3 Royal jelly production frame (Hu et al., 2019).

3. Larval transfer

First of all, an environment with a temperature of 30-35 °C and a humidity of 55-60% must be provided for successful larval transfer. It has been reported that success in vaccination will increase if a small amount of royal jelly diluted with distilled water at a ratio of 1:1 (v/v) is dropped into the queen cells in the larva transfer frame. Larval transfer is carried out by removing the 24-48-hours-old larvae at the base of the honeycomb cell unharmed with the help of a transfer spoon and leaving them unharmed in the queen cells with royal jelly droplets at the bottom.

4. Initiator colonies

Framed bee hives with abundant young bees are selected as the starter colony. Queens of starter colonies are taken. Then, the colony is checked and the natural queen cells are destroyed. The slats, whose larva transfer process is completed, are placed between the frames with the young worker bees in the prepared starter colonies. 2 frames can be used in each launcher. The initiator hive must have at least one open larvae frame between frames. In a production model of 25 hives, 6 starter colonies are needed. In the enterprise, the continuity of the 3-day production process is ensured by inoculating 2 starter beehives on a daily basis. There are 2 inoculation frames in each starter colony and 60 artificial queen cells in each frame. A total of 120 inoculations are required for 2 starter colonies per day. Feeding supplements should be given to these hives every day.

5. Finisher/Feeding hives:

Grafted frames remaining in the starter hives for 24 hours are removed and given to the feeding colonies by making the necessary sorting and arrangement. It is kept here for 36-48 hours. And then the harvest begins. In a production model of 25 hives, 3 feeding colonies are needed for sustainability. Feeding supplements should be given to these hives every day.

6. Harvest of royal jelly

The grafted frames, which have been kept in the feeding colony for a long time, are removed and the larvae in the queen cells are discarded. Then, the royal jelly at the base of the cells is put into opaque and dark colored glass bottles with a wooden/plastic spoon or vacuum (Figure 4) and kept in the refrigerator for max 4 months at +4 °C, and up to 24 months at -17 °C, without contact with light and oxygen. All factors such as the type of colony season, region, the strength of the colonies, the production and harvesting period of RJ, the provision of adequate nutrition, the use of larvae at the appropriate age, the number of larvae transferred at one time, the number of queen cells used in the colony, the age of the bees in the feeder colonies, the initial factors such as the number of young worker bees in the colony may concern efficient production of RJ (Yılmaz et al., 2017; Tagem, 2017).

Figure 4. Harvesting royal jelly (Yücel et al., 2017).

Conclusion

RJ continues to be the focus of attention from ancient times to the present day with its many therapeutic properties thanks to the bioactive components in its structure. Researches have indicated that royal jelly has vasodilator and hypotensive activities, antioxidant, antimicrobial, antidiabetic, antibiotic, disinfectant, and

antitumor effect, anti-hypercholesterolaemic activity and so on. As a result of small-scale beekeeping activities or larger volume production, RJ should be harvested without weakening the colony and damaging it. In recent years, royal jelly has attains a place in the market in different fields ranging from food to pharmacy, such as powder, paste, injection, tablet and capsule, frozen, royal jelly yogurt mixture, liquid preparations, honey and ginseng mixture, anti-aging creams and solutions. In great numbers of countries, preparates containing different amounts of royal jelly are arranged and sold, and many different functional products are developed with assorted compositions of bee products such as honey, pollen and bee venom. All this diversity is based on the valuable biological activities of RJ. In consequence, it is predicted that the production and consumption demand of royal jelly in the world will continue to increment.

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