Journal of Functional Foods 44 (2018) 255–264

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

A review on Royal Jelly proteins and peptides

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ARTICLE INFO

Keywords:
Royal Jelly
Hypopharyngeal gland
Mandibular glands
Major Royal Jelly proteins
Royalactin

ABSTRACT

Royal Jelly (RJ) is a nutrient rich substance secreted by the hypopharyngeal glands of young worker bees. Owing to the exceptional biological properties, RJ is used in pharmaceutical, food and cosmetics industries. Several studies vouch that RJ has anti-ageing, antibacterial, anti-fatigue, anti-inflammatory, antioxidant, antitumor, anti-diabetic and antimutagenic potentials. These activities are mainly attributed to bioactive components it contains.

One of the principal bioactive components is Major Royal Jelly Proteins (MRJPs) which is considered to be a major factor in honey bee queen development. In this review, we explore large number of studies that have been undertaken to elucidate the functions and characterization of Royal Jelly proteins and peptides.

1. Introduction

For millennia, products from honey bees have been used as food and medicine because of their high nutritive value and nutraceutical properties. Honey bees are a source not just for honey but for several other valuable natural products with cosmetic and health-promoting compounds such as bees wax, pollen, and Royal Jelly (RJ). Demand for these ingredients far exceeds supply.

2. Royal Jelly

RJ is a thick milky-white fluid produced and secreted by nurse honey bees (young newly emerged workers of 5–15 days old) from their hypopharyngeal gland (Fig. 1). It is fed to all the bee larvae in the early stages of their life and to the queen bee until she dies. After hatching, the larvae destined to be workers are fed with a mixture of RJ, honey and pollen (Snodgrass, 1984). Key nutrients in RJ and the duration of nourishment with it determine whether the female larvae develop into short-living infertile workers or the long-living fertile queen (Knecht & Kaatz, 1990). The infertile worker bees have a life span of approximately six to eight weeks, while the queen which is continually fed on RJ lives a fertile life of up to four to five years. Even though the queen and the workers are genetically identical they vary extensively in their phenotypic, physiological and functional characteristics. It is thus evident that RJ has a strong epigenetic influence in the differentiation of the larvae into the sub-populations of workers and queens. This is thought to be achieved by epigenetic modification to DNA and regulation of gene expression through methylation of CpG islands (Kucharski, Maleszka, Foret, & Maleszka, 2008). How RJ achieves this biological outcome is an enigma that scientists have not been able to convincingly answer despite numerous investigations and tests. On the basis of these observations numerous experiments have been carried out to investigate whether the effect of RJ is similar in organisms other than bees with respect to their development, maturation and longevity.

3. The source of Royal Jelly – the hypopharyngeal gland and the Mandibular gland

The hypopharyngeal gland (hpg) and the Mandibular gland (mbg) are the organs involved in the production of RJ. Mbg is a pair of sac like glands which is found only in queen and worker bee. It is located on both sides of the head, directly above the mandibles (Örösi-Ṕ l, 1957). Similar to hpg, RJ secretion by mbg also changes with age of worker bees (Huo et al., 2016). Hpg is a paired long tuberous organ located within the frontal part of the worker bee's head (Fig. 2). It has many small sac like structures called acini composed of secretory cells (Huang & Otis, 1989). The genes in these secretory cells temporally express a variety of proteins that regulate age (time) dependent changes in honey bees. These proteins are regulated by phosphorylation to optimize their cellular activity (Qi et al., 2015). The size of the acini increases around the 6th day after hatching coinciding with the very high rate of expression of RJ but is significantly reduced after the 15th day with the

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https://doi.org/10.1016/j.jff.2018.03.008
Received 30 December 2017; Received in revised form 4 March 2018; Accepted 4 March 2018

Fig. 1. Image of honey comb cell filled with Royal Jelly.

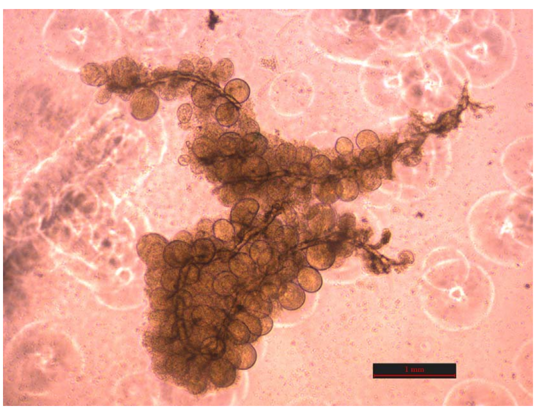

Fig. 2. Hypopharyngeal gland: Image from light microscopy.

colour changing from cream to pale yellow (Chanchao, Srimawong, & Wongsiri, 2006; Hrassnigg & Crailsheim, 1998; Huang & Otis, 1989; Liu, Wang, Zhou, & Zeng, 2015).

Both hpgs and mbgs produce RJ but only hpgs are involved in the production of proteins. Rate of protein synthesis in the hpg is thus highest in nurse bees and lowest in foragers (Knecht & Kaatz, 1990). This coincides with the synthesis and expression levels of protein rich RJ when the female worker bees are in the young nurse stage and the cessation of its expression when they start flying out as foragers.

When the bees become foragers, the glands shrink and switches to the expression of enzymes such as α-glucosidase, lucine arylamidase and invertase which are needed for the production of honey (Chanchao et al., 2006; Kubo et al., 1996; Simpson, Riedel, & Wilding, 1968; Suwannapong, Chaiwongwattanakul, & Benbow, 2010). Thus the foragers are no longer able to produce Royal Jelly.

For an apiculturist, on a bio-commercial perspective, a bio-technological intervention that succeeds in retaining a healthy honey bee colony will be advantageous in boosting the production of RJ.

4. Composition of Royal Jelly

RJ has a pH between 3.6 and 4.2. Water forms the major component at 60–70% (w/w) followed by proteins at 9–18% (w/w) and total sugars at 10–16% (w/w). It also contains small amounts of lipids, vitamins, salts and free amino acids (Bogdanov, 2011; Ramadan & Al-Ghamdi, 2012; Rembold & Dietz, 1966; Sabatini, Marcazzan, Caboni, Bogdanov, & Almeida-Muradian, 2009; Xue, Wu, & Wang, 2017).

The composition of RJ varies with seasons and ecological conditions around the location where the bees inhabit and forage. It also differs according to the race (Sano et al., 2004) and caste of the honey bee (Brouwers, Ebert, & Beetsma, 1987), physiological and metabolic differences between the nurse bees (Brouwers et al., 1987; Lercker, Caboni, Vecchi, Sabatini, & Nanetti, 1993), and the time of harvest of RJ (Scarselli et al., 2005; Zheng, Hu, & Dietemann, 2010).

Among the 9–18% proteins, majority of them are categorised as Major Royal Jelly Proteins (MRJPs), of which Major Royal Jelly Protein 1 (MRJP1) accounts for more than 45% (Furusawa et al., 2008). This is the most studied protein and considered to be the key factor that directs the development of the honey bee queen (Kamakura, 2011).

5. Proteins from Royal Jelly

Analyses of the Royal Jelly proteins show that 82–90% (w/w) is constituted by MRJPs (Drapeau, Albert, Kucharski, Prusko, & Maleszka, 2006; Santos et al., 2005; Schmitzova et al., 1998). Santos et al. (2005) and Shinkhede and Tembhare (2009) used evidence obtained through histological and transmission electron microscope studies to show that MRJPs are produced in the hpg of nurse bees. Apart from hpg, Buttstedt, Moritz, and Erler (2013a) also examined the expression of mrjps in various body parts (head, thorax and abdomen) of worker bees (nurse and foragers), queen bee (mated and unmated) and drones.

MRJPs are named by the order of the molecular weight or simply numbered according to the order in which they were discovered resulting in different names for the same proteins. MRJPs are named by the order of the molecular weight or simply numbered according to the order in which they were discovered resulting in different names for the same proteins. Table 1 shows the different names by which the major royal jelly proteins are known. Within the RJ protein family, nine members have been identified viz. MRJP1, MRJP2, MRJP3, MRJP4, MRJP5, MRJP6, MRJP7, MRJP8 and MRJP9 which are encoded by nine different genes. Fig. 3, briefly shows the classification and functions of MRJPs.

These complex proteins of MRJP family contain high amounts of amino acids necessary for nourishing both the queen bee and larvae. Arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine are the ten essential amino acids most commonly seen in MRJPs; with MRJP1 having 48%, MRJP2 having 47%, MRJP3 having 39.3%, MRJP4 having 44.5%, MRJP5 having 51.4%, MRJP6 having 42%, MRJP7 having 48.3%, MRJP8 having 49.5% and MRJP9 having 47.3% amino acid content. MRJP5 is rich in arginine and methionine while the predominant amino acids in MRJP1, MRJP2 and MRJP4 are leucine and valine. The major amino