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THE EFFECT OF ROYAL JELLY ON HORMONES DURİNG ADOLESCENCE

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review paper

Summary

Royal jelly is a unique food that is given in the honey bee colony from the egg to the maturity period of the queen bee, and only during the egg period of the other castes. Although both develop from a fertilized egg, the morphological and physiological differences between the worker bee and the queen bee are the result of royal jelly feeding. Royal jelly, which has many beneficial biological activities, has gained importance as a functional food. Scientific research has shown that royal jelly is effective on growth and sex hormones. Its effect on hormonal changes, especially during adolescence, should be taken into consideration, and hormonal changes that will occur in male and female individuals should be investigated.

Keywords: royal jelly, hormone, adolescence, infertility

Introductıon

Today, early puberty is one of the most important problems that concern parents regarding the growth and development of children. Early breast development, especially in girls, worries families. The cause of anxiety is early menstrual bleeding and the thought that growth will stop with bleeding. It covers the periods of adolescence, adolescence, and puberty. Adolescence covers the period between the ages of 10-21. This period is the transition period between childhood and adulthood, where physical, sexual, spiritual, and social changes occur. Puberty is the growth phase that includes physical and sexual maturation that occurs during adolescence. At puberty, secondary sex characteristics are acquired and with the completion of puberty, the person becomes capable of reproduction. The pubertal development process generally occurs between the ages of 8-13 in girls and between the ages of 9-14 in boys. The internal and external reproductive organs (ovaries, uterus, vagina, testicles, and penis) that are inherent in girls and boys constitute the primary sexual characteristics. In addition to the growth of these organs to reach adult sizes, physical changes such as hair growth and breast growth are defined as secondary sex characteristics. Adolescence is the transition period from childhood to adulthood, where secondary sexual characteristics and reproductive capacity are acquired. Puberty is early, starting before the age of 8 in girls and 9 in boys. If puberty does not begin when girls turn 13 and boys turn 14, there is a delay (Delemarre-van de Waal, 2002; Kuiri et al., 2011; Kirivanta et al., 2016; Sultan et al., 2018).
Under normal conditions, the ovaries and testicles, which are the female and male reproductive glands, produce female and male sex hormones (estrogen and testosterone). While the level of sex hormones is low in childhood, estrogen levels in girls and testosterone levels in boys increase dramatically during adolescence, and this increase reveals secondary sex characteristics. The stimulating effect that enables the awakening of the reproductive glands comes from the pituitary gland in the brain. The pituitary hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) stimulate the ovaries and testicles, ensuring the production of both hormones (estrogen, testosterone) and eggs (ovum and sperm) (Angold et. 1999; Mrug et al., 2014). Precocious puberty is the onset of secondary sex characteristics before the age of 8 in girls and 9 in boys. Breast growth or hair growth before the age of 8 in girls, and testicular growth and hair growth before the age of 9 in boys are considered early. Many factors affect the onset and progression of puberty, and genetic factors come first. In addition, racial-ethnic origin, socioeconomic conditions, geographical features, diet, obesity, endocrine disruptors, physical and psychological stress, and chronic diseases affect the onset of puberty. Natural or synthetic substances that have hormonal effects or affect the endocrine system by affecting the production, release, transport, or destruction of hormones are called endocrine disruptors. Natural endocrine disruptors include strawberries, soy products, carrots, apples, coffee, parsley, and legumes. Synthetic endocrine disruptors include DES (diethylstilbesterol), fungicides, herbicides, cleaning agents, polishes, cosmetic products, paints, and plastic materials. Consumption of non-organic agricultural products and living in constant contact with other endocrine disruptors from the development period in the womb may cause early puberty by affecting the brain, pituitary, and reproductive glands (Cassio et al., 1999; Lebrethon et al., 2000; Farello et al., 2019; Ridder et al., 1990; Mrug et al., 2014).

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Effect of royal jelly on hormones

Bee products are used to support the prevention and treatment of many diseases, and this form of treatment is called Apitherapy. Among the bee products, two products that have hormonal effects are royal jelly and apilarnil. Royal jelly is a bee product secreted from the hypopharyngeal (throat) and mandibular glands of young (5-15 days old) worker bees and is the only food that the queen bee feeds on throughout her life. It is a nutritious product with a creamy consistency, whitish, sharp phenolic odor, and a sour and bitter taste, used for the feeding of young larvae and the queen (Šver, 1996; Guo et al., 2021).

During the first four days, all fertilized bee eggs are fed with royal jelly and the queen bee can develop from all of them. However, queen bees are formed only from those fed with royal jelly during the entire larval development period. Due to this nutrition, significant differences are observed between queen bees and worker bees in many respects. While the reproductive organs of the queen bees, who complete their larval stage by being fed royal jelly in their morphological development, are well developed, the organs of the worker bees, such as the pollen basket, mandibles, brood gland, and wax glands, are well developed with the work done in the hive. As a result of this different nutrition for only 6 days, the queen bee gains resistance to diseases, can produce eggs twice its own weight (1500-3000) per day, and can live for 3-5 years. Worker bees, on the other hand, get sick more easily due to their weak immune systems, cannot lay eggs even though they are females, and live only 2-3 months. It is suggested that the main reason for this degree of differentiation between the two individuals is due to their feeding with royal jelly (Collazo et al., 2021).

The composition of royal jelly varies depending on the nutrition of the bees, season, age of the larva, and production method. The main components of royal jelly are 60-70% water, 9-18% proteins, 7-18% sugars, 3-8% lipids, minerals (Fe, Na, Ca, K, Zn, Mg, Mn and Cu), amino acids (Val, Leu, Ile, Thr, Met, Phe, Lys and Trp), vitamins (A, B complex, C and E), enzymes, hormones, polyphenols, nucleotides and small heterocyclic compounds. The pH value of fresh royal jelly is generally between 3.6 and 4.2. Royal jelly is a viscous, creamy, acidic, white-yellow-colored bee product with a pungent odor and sour-sweet taste. Royal jelly is relatively water-soluble and has a density of 1.1 g/mL. Changes in chemical compositions; it is caused by differences in different feeding (without sugars and/or protein supplements), production methods, environmental conditions, flora, bee breed, storage, and processing conditions (Rembold and Dietz, 1996; Xue et al., 2017).

The most important and basic component of royal jelly is 10-hydroxy-2-decanoic acid (10-HDA), which is a fatty acid. This component is the most important value that determines the quality parameter of royal jelly and is only found in royal jelly. Fresh royal jelly produced under appropriate conditions should contain at least 1.40% 10-HDA (Yavuz and Gürel, 2017).

The most important feature of royal jelly is that it is effective in cell renewal, production, and metabolism in the body. It gives the organism strength and vitality, allowing it to renew itself. Studies on these subjects in insects, birds, and mammals have found that it significantly increases lifespan. Royal jelly has cholesterol-lowering, blood pressure-lowering, and vasodilator activity. In addition, it has a hypoglycemic (lowering blood sugar) effect because it contains insulin and similar peptides, and an immunological effect because it is antimicrobial. Since it has a cell-repairing and rejuvenating effect, it is used to heal skin and hair diseases and regulate sexual functions. It is used as a regulator of abnormalities caused by chronic diseases, loss of appetite, and irregular and unbalanced nutrition. It is also recommended to reduce the possible harm of drugs used in the treatment of chronic diseases to the liver and kidneys and to protect these organs (Khazaei et al., 2017).

Many studies are showing the effect of royal jelly on infertility. For example, hydroxyurea (HDU), a class of antineoplastic drugs, has many adverse effects, including infertility, especially in men. Therefore, Tohamy et al. (2019) investigated the chemoprotective potential of royal jelly on HDU-induced testicular damage in their study. Experimental animals were given HDU (225 or 450 mg kg) before royal jelly (100 mg/kg) for 60 days. In a dose-dependent manner, sperm count and motility, as well as testosterone, GSH, and catalase concentrations, decreased in the hydroxyurea groups, while MDA, FSH, LH, IL-6, and IFNγ expression levels increased. In hydroxyurea-administered rats, royal jelly intake successfully improved sperm quality, hormonal and antioxidant status, and reproductive organ histochemistry. Researchers concluded that royal jelly can be used as an adjuvant drug to improve hydroxyurea-induced male subfertility, thanks to its antioxidant and anti-inflammatory activities. In another study, Nasir et al. (2017) investigated the effect of royal jelly in protecting rat testicles against carbon tetrachloride-induced testicular damage in male Wistar rats. Royal jelly was given to animals treated with Kabron tetrachloride at doses of 150 and 300 mg/kg. At the end of the experiment (50 days), a significant decrease in sperm concentration, sperm viability, and sperm motility and an increase in sperm abnormalities were observed in the group treated with carbon tetrachloride, while a significant decrease in sperm abnormalities was determined in the rat groups treated with royal jelly at both doses. In addition, while a significant decrease in sex hormone levels (T, LH, FSH) was observed in the rat group given only CCl_4 in the study, it was suggested that royal jelly could be used in the treatment of infertility problems in men due to the improvement it provided in the examined parameters. In studies conducted on farm animals, royal jelly increased the in vitro fertilization capacity of bull sperm. Consumption of royal jelly increased glycolysis, pentose phosphate pathway, and antioxidant enzyme activity in oocyte and cumulus cells, resulting in higher levels of oocyte maturation, fertilization, and blastocyst formation. It significantly increased sperm motility, luteinizing hormones, and testosterone levels in infertile men. Long-term and regular use of royal jelly stopped the age-related decrease in testicular function of male hamsters and stimulated testosterone levels and spermatogenesis. The consumption of honey and royal jelly together has been beneficial in the treatment of infertility due to asthenozoospermia. In a study examining the effect of tris-yolk extender supplemented with royal jelly on chilled and frozen-thawed ram semen parameters, frozen-thawed sperm total motility, progressive motility, membrane integrity, and viability were found to be significantly higher in the 3% royal jelly-supplemented group. Research shows that royal jelly may be effective in increasing male hormones and sperm count, as well as reducing reproductive toxicity. It has been reported that royal jelly application (gavage 100 mg/kg/day) increases epididymal sperm motility and in vitro fertilization capacity in adult male mice. However, some studies have shown that royal jelly can improve oxidative stress, and male infertility, and inhibit cell proliferation by breaking E2-induced signals. Ahmed et al. (2018) investigated the protective potential of royal jelly against cadmium-induced testicular dysfunction in rats. The royal jelly concentration used in the study was 100 mg/kg and serum and tissue samples were collected and analyzed after the 56^{th} day of the experiment. Results showed decreased serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), superoxide dismutase, glutathione reductase, sperm motility and count, and increased levels of malondialdehyde, nitric oxide, tumor necrosis factor-α (TNF-α). Abnormalities with severely damaged seminiferous tubule epithelium with cytoplasmic and nuclear disruptions were observed after cadmium toxicity, including testicular mRNA expression of TNF-α, steroidogenic acute regulatory protein, cytochrome P450 cholesterol side chain cleavage enzyme androgen binding protein, FSH-receptor, LH-receptor. Adverse changes in the androgen receptor, 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, and cytochrome P450 17A1 were significantly reduced by royal jelly application. Researchers concluded that royal jelly protects against cadmium-induced testicular toxicity. In another study on infertility, Al-Dujaily et al. (2019) determined the role of royal jelly on some sperm function parameters of obstructive azoospermic men and concluded that royal jelly strongly increased some sperm function parameters of vasectomized male mice. Researchers have suggested the possibility of using royal jelly for male factor infertility, especially in those with obstructive azoospermia.

Spermatogenesis and hormone secretions are very important endocrine and physiological processes to sustain life. In a study on the effects of royal jelly on the testicular development of offspring during neonatal and adolescence consumption, Shi et al. (2019) detected neonatal sexual hormone concentration and histopathological changes in the testicular development of male offspring after orally administering freeze-dried royal jelly to mice for 35 days. Male offspring were given 125, 250, and 500 mg/kg/day royal jelly. Weaned male puppies were given freeze-dried royal jelly for 35 days. It was determined that the diameter of the seminiferous tubule, the height of the seminiferous epithelium, and testicular weight increased significantly in the group given 250 mg/kg/day of royal jelly, while a high dose of royal jelly (500 mg/kg/day) decreased the diameter of the seminiferous tubule, but increased the height of the seminiferous epithelium of male offspring. Moreover, royal jelly administration (250 mg/kg) significantly increased testicular weight and spermatogenesis on the 21st day after birth, while high-dose royal jelly (500 mg/kg) treatment reduced the diameter of the seminiferous tubule and the height of the seminiferous epithelium. On the 35^{th} day after birth, 250 mg/kg royal jelly increased testicular weight, seminiferous tubule diameter, and FSH level. High-dose royal jelly, on the other hand, reduced testicular weight and size (seminiferous tubule diameter and seminiferous epithelium height), apoptotic germ cell rate, and all parameters of missing spermatogenesis. Apart from these, royal jelly (at all doses) reduced sexual hormone secretions (FSH, LH, E2) on the 21^{st} day after birth. The results obtained showed that oral administration of low and medium doses of royal jelly can increase testicular development in the neonatal period until adulthood, but the negative side effects caused by high doses of royal jelly may continue.

In recent years, families often use royal jelly supplements to help their children grow. Pirgon et al. (2019) evaluated the effects of royal jelly supplementation on the growth volume of young rats and hormone levels such as estradiol, growth hormone (GH), and insulin-like growth factor-1 (IGF 1). In the study, 7-day-old rats were given 50 mg/kg royal jelly via gavage once a day for 15 days. Plasma estradiol, growth hormone (GH), and IGF-I levels were then measured. Average weight and tail length changes were found to be significantly higher in the royal jelly group than in the control group at the end of the study. Plasma growth hormone and estradiol levels increased significantly in the royal jelly group, and the total height of the growth plate was found to be significantly higher in the royal jelly group than in the control group. Moreover, the percentage of estrogen receptor expression in the growth plate was expressed as 81.3% in the proliferative zone of the royal jelly group and 14.3% in the control group. Researchers have shown that royal jelly administration causes longitudinal bone growth as well as estradiol and growth hormone levels, but the findings also provide evidence that royal jelly has some potential estrogenic effects on growth. Bee products have been used to treat various human diseases for decades. It is known that major royal jelly proteins (82-90%), which are the most important bioactive components found in royal jelly, are potential factors in extending honeybee lifespan. Analysis of royal jelly proteins has shown that they consist of some essential free amino acids and complex proteins of the MRJP family, which are necessary for feeding both the queen and the larvae. Some studies show that royal jelly has an estrogenic activity similar to exogenous steroid hormones, including testosterone and 17β-estradiol. These estrogen-like compounds may exert various estrogenic or anti-estrogenic effects in the reproductive systems, commonly by modulating estrogen receptors (ER). Exogenous estrogen or estrogen-like compounds can be found in many foods of plant and animal origin, such as seeds, vegetables, milk, and dairy products. It is also reported that royal jelly prevents the negative effects of exogenous estrogen on the male reproductive system. Studies on reproduction have shown that royal jelly can exert estrogenic effects in vivo and in vitro. It is very important to investigate the reproductive function of offspring when exposed to royal jelly continuously from newborn to maturity.

Sosa-Perez et al. (2017) investigated the effect of intravenous administration of 500 mg royal jelly for seven days before progestogen termination on the synchronization, onset, and duration of estrus, follicular population, and ovulation rate of Pelibuey sheep. Researchers reported that royal jelly could be an alternative for the reproductive management of sheep production units, as it reduces the time to the onset of estrus and increases the number of follicles > 4 mm and the ovulation rate in Pelibuey sheep. Al-Eisa et al. (2018) investigated the protective effect of royal jelly against aluminum chloride ($AlCl_3$) toxicity on testicular histology as well as on pituitary, thyroid, and sex hormones. Animals were given aluminum chloride ($AlCl_3$) (30 mg/kg) intraperitoneally every day for eight weeks, and royal jelly (400 mg/kg) was given once a day in drinking water for eight weeks. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), percentage of triiodothyronine to thyroxine (T3/T4) and testosterone level were measured in blood serum. Aluminum chloride; It caused a significant decrease in FSH, LH, TSH, T4, T3, T3/T4, and testosterone, while causing the development of oligospermia, hypoplasia, blocked blood vessels, and exfoliated tubules in the testicles. However, royal jelly completely cured these effects.

In a study on male infertility in 2007, royal jelly was given in different doses (25 mg, 50 mg, 100 mg) to 83 infertile men. As a result of the data obtained, it was reported that sperm motility, sluggish sperm, sexual intercourse/week, testosterone level, and LH hormone level increased in infertile men who used royal jelly for three months. The study showed that royal jelly application is safe, has no side effects, and is effective in the treatment of male infertility (Al-Sanafi et al., 2007).

In a study conducted in Egypt, the mid-cycle effectiveness of intravaginal applications of Egyptian bee honey and royal jelly mixture for the treatment of infertility due to asthenozoospermia (low sperm motility) was evaluated on 99 couples. For the research, 3 g of royal jelly and 1 teaspoon of bee bread were added to 100 g of Egyptian honey, and the mixture was given at least 3 days after preparation to ensure sufficient enzymatic interaction between the honey and bee bread. Before use, the mixture was diluted 1:1 in a normal saline solution and then self-administered intravaginally at each coital act starting 1 day after the last menstruation. In this application, repeated for 2 weeks, a plastic piston applicator or a 10 ml syringe was used to introduce the mixture. The application was performed precoital or postcoital, depending on the preference of the couple. 50 couples were studied in this group and 49 couples in the intrauterine insemination group. At the end of the study, a total of 553 cycles were analyzed and it was revealed that there was a significant difference between honey and royal jelly application and vaccination groups. It has been observed that honey and royal jelly application is more effective in the pregnancy cycle. It has been reported that intravaginal use of honey-royal jelly mixture may be a simple and reasonably effective method in the treatment of asthenozoospermia (Abdelhafiz and Muhamad, 2008).

Yang et al. (2012) administered doses of 200, 400, and 800 mg/kg/day to rats for 4 weeks, sperm deformity increased and serum hormone levels were affected in the high-dose group. After the royal jelly administration was stopped, the values returned to normal levels. El-Eisa et al. (2017) determined the effects of royal jelly on pituitary, thyroid, and sex hormones against aluminum chloride toxicity. While aluminum chloride harmed FSH, LH, and TSH hormones when 400 mg/kg of royal jelly was given for eight weeks, royal jelly alleviated these negative effects. Spermatogenesis and hormone secretions are very important endocrine and physiological processes for the maintenance of life. The effects of royal jelly on the testicular development of offspring during neonatal and adolescence have not been adequately studied. Shi et al. (2019) determined neonatal sexual hormone concentration and histopathological changes in testicular development of male rats after oral consumption of lyophilized RJ (125,250 and 500 mg/kg/day) for 35 days. At the end of the study, they determined that oral M-RJ (250 mg/kg/day) administration significantly increased testicular weight (on the 14^{th} day, the diameter of the seminiferous tubule and the height of the seminiferous epithelium of baby mice. However, high dose RJ (500 mg/kg/day) day) decreased the diameter of the seminiferous tubule but increased the height of the seminiferous epithelium of male offspring. RJ significantly increased testicular weight and spermatogenesis on day 21. On the contrary, oral H-RJ treatment significantly increased the diameter of the seminiferous tubule and the height of the seminiferous epithelium in PNDs on day 21. decreased ($p<0.05$). Oral M-RJ treatment on PND day 35 increased testicular weight, seminiferous tubule diameter, and FSH level. In addition, sexual hormone secretions (FSH, LH, E2) increased significantly after RJ treatment (L-) on day 21, respectively. They concluded that oral administration of low and moderate doses of RJ could enhance testicular development in the neonatal period until puberty, but negative side effects caused by high doses of RJ may remain.

Ghanbari et al. (2018) stated that uterine and ovarian weights and progesterone and estradiol serum levels in immature rats increased in the experimental groups compared to the control group. Additionally, they identified a significant increase in the number of mature follicles and corpora lutea in rats receiving RJ compared to controls. Researchers have reported that Royal Jelly promotes folliculogenesis and increases ovarian hormones. They also stated that it can be considered a natural growth stimulant for immature female animals.

In a study on male infertility in 2007, royal jelly was given in different doses (25 mg, 50 mg, 100 mg) to 83 infertile men. As a result of the data obtained, it was reported that sperm motility, sluggish sperm, sexual intercourse/week, testosterone level and LH hormone level increased in infertile men who used royal jelly for three months. The study showed that royal jelly application is safe, has no side effects, and is effective in the treatment of male infertility (Al-Sanafi et al., 2007).

Conclusıon

Royal jelly is a bee product that contains hormones as well as rich nutritional elements and biomolecules. For this reason, the effect mechanisms of royal jelly on the endocrine system should be considered in many aspects. Its effect on hormonal changes, especially during adolescence, should be taken into consideration, and hormonal changes that will occur in male and female individuals should be investigated. Gynecomastia and early menstruation are just some of these effects.

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