

Impact of Royal Jelly on Infertility: A Review

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ABSTRACT

Royal Jelly (RJ) is most wanted healthy food supplement that makes lots of health benefits. One of the benefits include that it can act as potent supplement for healthy egg to help women with infertility. This review is focused on the recent developments in use of RJ in the treatment of infertility and boon for them to give a dream child. The healthy egg is very phenomenal key factor for the *in vitro* fertilization to be successful in sexing with sperm. RJ is traditionally used as health supplement for infertility treatment from the ancient time in Indian traditional system. The recent literature revealed that, scientific and traditional findings are proven it RJ is one of the therapeutic molecule and act as a food supplements that can be used it in to improve egg cell physiology. Although, there is no clinical research studies have been reported yet on RJ. Hence, in this review explored the comprehensive report on health benefits of RJ and its impact on reproductive aspects in particular in egg development of women during ovulation. This article will be the key step to the researchers and scientists who are involved in searching alternative, cost effective and without side effect for treating infertility in global scenario.

Key words: Royal Jelly, Infertility, Fertilization, Egg, Sperm, Clinical, Health, Cell.

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INTRODUCTION

Royal Jelly (RJ), is predominantly secreted in between the sixth and twelfth days of workers honeybees hives and it is secreted from the hypo pharyngeal and mandibular glands of honeybees (*Apis mellifera* and *Apis cerana*).^[1] RJ is an important food source which helps in the growth and development of queen honeybee. Multiple benefits could be considered for queen bees, including large size (double that of working honeybees), functioning sexual organs, durability (about 5–6 years, though 35–40 days).^[2,3] RJ mainly consists of organic and health-promoting components such as proteins, lipids, fats, vitamins, minerals and amino acids.^[4] It is a good source of vitamin generally comprises of riboflavin, thiamine, niacin,

folic acid, biotin and pyridoxine and smaller quantities of Vitamins C, D, A and E.^[5] In addition, the major minerals in RJ are calcium, sodium, potassium, copper, iron, zinc and manganese.^[6] One of the key bioactive compounds of RJ is 10-hydroxy-trans-2-decenoic acid (10HDA), an unsaturated fatty acid found in natural source, especially in RJ.^[7] Generally in RJ, different biological activities depend on the type of cells;^[8,9] for example, its 10HDA has important anticancer activity.^[10] Shakhoun (queen cell), a frame made of waxed bees and filled with RJ, is the honey bee larva's spot. RJ plays a key role in the feeding and growth of larvae into a long-term, fertile mature queen of honey bee (Figure 1).^[11] Furthermore, RJ has long been used as a dietary, anti-aging or infertility supplement as a therapeutic medicine.^[12] In laboratory animals, RJ has been shown to have several pharmacological functions, like antitumor,^[13] antioxidant,^[4] anti-inflammatory,^[14] antibacterial,^[15] anti-allergic,^[16] anti-aging^[17] and anti-hypertensive properties.^[18] For humans, its oral consumption facilitates the metabolism of lipoproteins and decreases the levels of total serum cholesterol (TC) and low density

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Figure 1: Developing Queen Larvae Surrounded by Royal Jelly in open Queen Cel.^[11]

lipoprotein (LDL). In postmenopausal women, a mixture of four natural components, including RJ, promoted health and well-being.^[19] With this literature our aim of study to explore the RJ on fertility research for covering various model organisms for the developmental and reproductive activities with the available research reviews with special reference to infertility treatment.

Infertility is described as the inability to conceive after one year of continuous unprotected intercourse. Infertility is a degree of sub fertility in which 1 in 7 couples require specialist support to conceive. Sub fertility may be either primary or secondary. Primary sub fertility is a pause for a couple who had no prior pregnancies; and secondary sub fertility is previously, although, for example, miscarriage, ectopic pregnancy and the pregnancy might not be a successful one.^[20]

Both male and female are equally responsible for infertility. Most infertile spouses have one of these three major causes, involving male factor, tubal-peritoneal disease and ovulatory dysfunction^[21] so different therapeutic approaches have been used to enhance reproductive capacity. Natural supplements, have commonly been applied to improve health and well-being in the world population and may be a successful treatment for the reproductive issues.^[22] RJ has been used in China as a food and medicine.^[23] Lewis^[24] and Abdelnour *et al.*^[25] reported that RJ has been correlated with positive effect on human fertility, because it is successful on osteoporosis, premenopausal symptoms and enhances hormonal balance and fertility by increasing the quality of sperm and ova in both men and women. The RJ significantly increased the amount of ejaculates, seminal fructose, sperm motility and sperm counts in buck semen, along with serum testosterone levels.^[26] In buffalo semen, it also showed that the frozen diluents combined with RJ improved the frozen-thawed

sperm quality.^[27] Study found out that during storage of sperm in cold temperature its motility and plasma membrane integrity has improved by addition of low level concentration of fresh RJ (as an antioxidant source).^[28] RJ forms gonads in the queen bee. An RJ diet induced higher levels of testosterone (T) and more active spermatogenesis in hamster testing^[29] and increased levels of serum testosterone in heat stressed male rabbits.^[30] In humans it can also modulate the sex hormones for the needful physiological function during the fertility activities.

This study was performed by the comprehensive activity to explore the data of RJ in animal and human for infertility treatment and their pros and cons by the researchers. Data were selected after the primary survey of all the abstracts and the most relevant articles were chosen to be read it in full to review it systematically for the current study.

Historical view

Historical documents of human RJ feeding date back to ancient Greece for the first time, where Greeks believed that the “ambrosia,” the nectar that offered immortality to the gods of Olympus, was created in part by the RJ. Ancient Egyptians used the RJ as a cosmetic, resulting in Cleopatra’s reputation as one of the secrets of her personal beauty. In addition, during that era the RJ was a symbol of the Pharaohs’ majesty and strength that usually ate RJ.^[31] RJ is a fragment of the key food source diet for honey bee larvae and plays a major role in the caste identification of this genus,^[32] with special protein and phytochemicals rich in secondary metabolites.^[33-35] RJ has been well known as a natural product in the traditional remedy since ancient times in the Chinese civilization. Furthermore RJ, was developed in some sovereign gardens was associated with the sexual strength and longevity of China’s ancient dynasties, even in old age.^[31] Usage of RJ as a health enhancer and functional drug has been explored since the early 1960s with the introduction of “Apitherapy”. Since then, the features of RJ have been discovered and widely used for human and animal remedies.^[25,31,36] Regular intake of RJ is generally thought to have beneficial effects on many medical ailments, such as Alzheimer’s, depression, infertility, digestive problems, aging, anemia, stress-related illnesses and weakened immune function, as well as antidiarrheal, antineoplastic, antioxidant, antibiotic and anti-inflammatory properties.^[37,34] RJ was also proposed as a dietary supplement to boost the various problems with fertility.^[37,38]

Demography of Infertility

Infertility and subfertility affect a large proportion of human population. World Health Organization^[39] has estimated that more than 10 percent of women were afflicted people who have attempted unsuccessfully and remained in a constant relationship for five years or forever. For the pregnancy, women's wait for the two year time frame for positive result, but due to negative impact of infertility prevalence levels increasing significantly in the global population. The pressure is still unknown for males compared to female population to become victim for the sterility. The overall fertility consequences are high, possibly underestimated and has shown not reduction in the last 20 years.

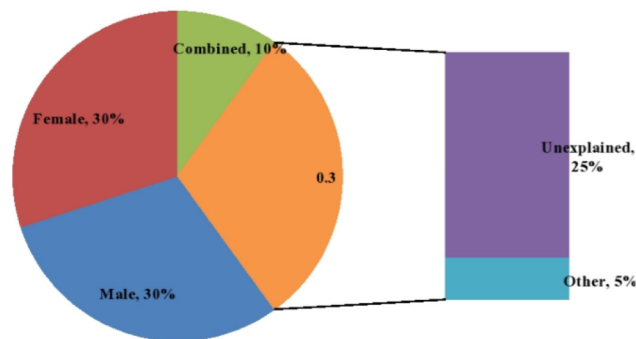
In India, the second most populous nation in the world with 1.3 billion people after China (1.4 billion) has always been intrigued by demographers. And now, with the United Nations showing to outstrip India's population as early as 2022, it looks like the country explodes the population it seems. According to The World Population Prospects: The 2017 Revision report estimates that the Indian fertility rate (as measured by the number of children born) has decreased by more than 50%, from 4.97 in the 1975-80 periods to 2.3 in the current 2015-20 period. By 2025-30, the projected rate will continue to be 2.1, reaching 1.86 from 2045-50 and 1.78 from 2095-2100. Infertility currently affects about 10 to 14 percent of the Indian population, with higher incidence in urban areas where one out of six couples were affected, according to the Indian Society of Assisted Reproduction (ISAR). In recent studies shows that, 27.5 million couples in India actively attempting to conceive again and again due to infertility problems.

In this scenario, present and future infertility work does not only support itself (Figure 2) following consequences are most essential to critically think and taken step towards the solution by using such resources.

1. Help in finding innovations for new methods of contraception without any side effect and will be always withdrawal impact.
2. Help resolve recurrent spontaneous miscarriages and identify the why such incidence occurs
3. Help in addressing complications related to pre-birth or other neonatal complications during pregnancy.
4. Help also to ensure zero (horizontal and vertical) transmission of sexually transmitted diseases (STD) and human immunodeficiency virus (HIV) infection.

Realization research is needed in developed countries where the global burden of infertility is increased, assuring:

Infertility Cases



[Sources: <http://www.eggdonors.asia-blog/infertility-common-causes/>]

Figure 2: Infertility common causes statistics.

greater focus on secure, cost-effective solutions and innovative; and better implementation and integration of diagnosis, monitoring and treatment of access to subfertility/infertility.

In this context, there are a variety of different “super foods” act as natural resource that have proved to be highly successful in helping with fertility problems by RJ, it is the reigning King or Queen of the bough product as a boon for the resolve the reproductive issues. This natural medication has been discovered by scientists to treat infertility that is safe and healthier and cost-effective.

Research findings and outcomes on RJ on animals and humans

Ahmadnia *et al.*^[40] has been performed an experiment using RJ. In this experimental study, thirty male adult rats of 60 day old were used. Once a day, the control group consumed 400mg/kg only honey by special syringe. While, the other group consumed the same amount of RJ composed of honey by the same dose. Then the blood samples of carotid arteries were obtained in dry tubes. By centrifugation serum was obtained and sent for sexual hormone assay Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH) and testosterone. The consumption of RJ have a significant effect on sperm count. The mean sperm count in case group was approximately 5 times more than control group and sperm motility was significantly effective and progressive in case group. Also the leydig cell count was obviously more in the group used RJ. Using RJ had no effect on LH, FSH and testosterone serum level. In another study performed on rats in China by Yang and his colleagues, their results showed using RJ has no significant effect on sperm count.^[41] They evaluated the effect of RJ on histology of testis, spermogram parameters and sexual hormones in male rats carefully, but it is due to

low concentration. Findings of such experiment on animal models may not be have high impact compare to human, consumption of RJ 100% concentration would be useful for infertile men suffering idiopathic azoospermia, oligospermia and asthenospermia.

Similar findings along with lithium carbonate also studied in adult male mice to impair and check the sperm parameters with and without RJ in 250mg/kg body weight. The result exhibited with lithium carbonate significant reduction in the total sperm count as compared to control by impacting on decline in sperm motility (%), viability, sperm life (%) and abnormal sperm (%) were significant. Whereas, lithium carbonate + RJ administration were non-significant in total sperm count as compared to control and the motility (%), viability and sperm life (%) were significantly increased. By this outcome, the protective effect of RJ administration may be used in combination with lower concentration of lithium carbonate to recover male fertility.^[42]

Ghanbari *et al.*^[43] proved it as RJ can be used as complementary diet and prescribing it widely by traditional medicine concept for infertility treatment. In their study planned to evaluate the effects of RJ on hormonal, ovarian components and antioxidants in immature female rats. The experimental groups received 100, 200 and 400 mg/kg/body weight/daily in the dose level of RJ for 14 day duration. The body weights were increased significantly in all the RJ treated animals even though by the age differences. Uterine, ovarian weights, serum levels of progesterone and estradiol were increased significantly in treated groups compared to that of control also exhibited follicular changes compared to that of control. Antioxidant study of serum levels in Ferric Reducing Antioxidant Power (FRAP) increased whereas Nitrous Oxide (NO) decreased significantly. RJ promotes follicular development and increase in ovarian hormones, due to that, the RJ can be considered as a natural product for growth stimulator in immature or infertile female animals.

Another group of scientists^[44] also worked on effect of RJ on fertility and biochemical parameter in bleomycin (BL) induces in male rats. Treatment of BL significantly decreased sperm count, sperm viability, motility and testosterone level compared to control, in other group treated with RJ significantly increased the immature sperm, deoxyribose nucleic acid (DNA) damaged sperm and concentration of malondialdehyde (MDA) were exhibited when compare to control and RJ+BL group. RJ was highly effective by bleomycin-induced toxicity on all the reproductive parameters.

The experimental findings of BL shows negative impact on function of the male reproduction in matured. RJ

is a complex antioxidant potential due to that it has beneficial biological properties on their findings as fertility enhancer. Hence, RJ could prevent testicular toxicity due to BL treatment. RJ has a withdrawal effect and possible protection against BL-induced toxicity with sperm parameters when administered after BL to the animals.

Gimenez-Diaz *et al.*^[45] studied on improved reproductive response of sheep in intrauterine insemination program with the use of RJ. For the 30 and 60 mg natural progesterone treated groups, estrous (30.5%) and conception rates (50% for both treatments) significantly not much increased. Ewes that received 300 IU equine chorionic gonadotropin (eCG) + 500 mg RJ to check the synergistic effect and higher conception rates (47.6%) higher than that of treated only eCG in a 300 or 600 IU (40.0%) at sponge removal. There was a significant delay in estrus phase onset of ewes which was received 100 IU eCG + 500 mg RJ when compare to other groups. Induction of estrus with vaginal sponges impregnated by usage of natural progesterone and RJ-eCG synergistic effect resulted in adequate conception output in ewes inseminated by laparoscopically. Single dose of 500 mg RJ was effective and significant and easy way to increase all the reproductive parameters in the anestrus season to act as seasonal sheep breeder. In addition research should focus on specifically ovarian activities using RJ along with eCG administration to ewes.

In another findings, Kohguchi *et al.*^[28] again shown the effect of RJ as diet on the testicular functions on hamsters. To know the long-term administration of feeding RJ to investigate the testicular function on 32 week old golden male hamsters were studied at the dose of 50 ug/g diet or 500 ug/g diet for the 12 week duration. RJ diet groups showed higher testosterone levels and more concentrated spermatogenic elements than the control and effect depends on dosage. The concentration of spermatogenic elements and testosterone level in the 500 ug/g treated with RJ diet showed significantly changed compared control groups. These findings indicate that RJ administration in long-term feeding on age-associated male hamster's resulted in decline of testicular function.

Results of the feeding 500 ug of RJ/g inhibited significantly lipid peroxidase (LPO) concentration compared to control hamsters. The outcome of the RJ administration in long time inhibited LPO and protects the organs from free radical-induced cellular damage. Due to free radical scavenging function, RJ acts as antioxidant and helps in male gonads for hormonal regulation and also reduced the function of testicles. Further research studies require investigating

the involved molecular mechanisms. These reports demonstrated first time that the long time administration of RJ inhibited the testicular function of male hamsters. By these evidences researchers are not only worked in animals, with the positive impact of RJ tried for infertility issue in humans. Al-Snafi *et al.*^[46] had worked on effect of RJ on male infertility. In their study used 83 infertile men and treated with RJ in 10gm pure honey, in 1st group treated with the 100mg concentration for 22 peoples, in 2nd group treated 50mg concentration for 21 peoples, in 3rd group treated 25mg concentration for 20 peoples and in 4th group treated 10gm pure honey only for 20 peoples for 3 month duration. The findings of the study state that, treatments were safe and no side effects were observed. In findings revealed that active sperm motility, testosterone content, LH content, motility of the sperm and activity of the intercourse / week significantly increased in infertile men during the treatment of RJ also found non-significant change in sperm count and FSH concentration. These findings were proven statistically RJ treatment depends upon dose and concentration to be effective and safer in the infertility therapeutic solution.

CONCLUSION

In conclusion, due to its promising medical and nutritional purposes, Royal Jelly (RJ) is one of the most valuable therapeutic products listed by natural medicine scientists. It has been shown that daily intake of the high-quality RJ helps regulate hormones. It makes it helpful for those individuals who suffer from a hormonal imbalance, as it helps to benefit the endocrine system. This can also assist with problems relating to fertility in relation to hormonal imbalance. RJ intake can increase the genital parameters in particular the sperm count and motility could also be beneficial on the microscopic structure of the testis by growing the mature and active cells. These results should be useful for infertile men who have low sperm counts and poor sperm motility to help with fertility. Not only with animal but from this review we can conclude RJ have a great impact in human life also. Thought more studies can be done on this great natural source.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

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