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Original article

A folk remedy: royal jelly improves lung capacity in smokers

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Summary. *Background and Aim:* Royal jelly (RJ) is one of the natural, valuable curative bee productdue to its promising health-beneficial and nutritional properties. This healthy diet possesses anti-inflammatory, antimicrobial, antioxidants, antitumor, and immunomodulatory functions which benefit in humans health and welfare,resulting in its widespread medical use. The aim of this randomized case controlled study was to determine the effect of royal jelly on the lung capacity of sedentary male smokers. *Materials and Methods:* The study was approved by the ethics committee of the university and consisted of 83 sedentary male and single participants aged 25-30 years without any health problems. Participation was voluntary. This case controlled design study was conducted in accordance with the ethical principles outlined by the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from participants. The sample was divided into four groups: smoker experimental (Group I: 22), non-smoker experimental (Group II: 21), smoker control (Group III: 20), and non-smoker control (Group IV: 20). The experimental groups consumed 1000 mg/day pure royal jelly between 08.00 and 10.00 am for 21 days. The control groups consumed a placebo liquid between 08.00 and 10.00 am for 21 days. Pre- and post-pulmonary function tests (PFTs) were performed. *Results:* Group I had significantly higher mean posttestforced expiratory volume in one second(FEV1) (1.86±0.19 L) than mean pretest FEV1 (1.76±0.05 L) while Group II had significantly higher mean posttest FEV1 (2.25±0.27 L) than mean pretest FEV1 (2.18±0.17 L) ($p < 0.000$). No statistically significant difference was observed in the control groups. *Conclusion*: PFT results before and after 1000mg/day royal jelly supplement revealed positive and significant differences.

Key words: royal jelly, sedentary, smoking, pulmonary function tests, FEV1

Introduction

Royal jelly is a substance secreted by honey bees to feed especially the queen larvae, hence the name royal jelly. Its health benefits were discovered in the 1600s. Royal jelly is a secretion of the hypopharyngeal glands of 5-10-day-old honeybee workers. It is pellet-like and has a distinct smell and bitter taste. Worker bees begin to synthesize protein in the hypopharyngeal glands about four days after they are hatched. Protein synthesis continues to increase for eight days, reaches its maximum level on the fourteenth day and starts to decrease from the seventeenth day on (1, 2). Royal jelly is milky when secreted and delivered to the oral cavity but it turns dark and creamy after being placed in honeycomb cells. It is a yogurt-like homogeneous substance with the consistency of a fluid paste which, however, becomes more viscous when stored at room temperature or in a refrigerator at 5°C. It contains proteins, lipids, carbohydrates, ash, P, Na, K, Ca, Mg, pollen, and C, D and E and B, and many other vitamins (3, 4).

It also contains 10-hydroxydecanoic acid (10-HDAA), 10-hydroxydecanoic acid (10-HDAA) and sebacic acid (SEA) which exhibit broad-spectrum activity against numerous bacteria and fungi (5). The proteins in royal jelly are antioxidants used in the treatment of such diseases as cancer, atherosclerosis, hypertension, infertility, asthma, depression, and diabetes mellitus resulting

from oxidative stress caused by the imbalance between reactive oxygen species (6). It also plays a key role in cell renewal, regeneration, and organization, and antiaging, and lowers blood cholesterol, total lipid, phospholipid, triglyceride, beta lipoprotein levels, and blood pressure, and dilates vessels. It has also been reported for many years that royal jelly exhibits antimicrobial and insulin-like hypoglycemic and immunological activities, has therapeutic properties for skin and hair, and reproductive diseases, regulates sexual functions, and repairs and rejuvenates cells (7-9).

Royal jelly is used more and more in daily diet and in the treatment of many diseases. With these superior properties, royal jelly is becoming increasingly important for health and is studied more extensively.

Smoking increases airway resistance during respiration. Thenicotine in cigarettes causes bronchioles to contract, and carbon monoxide in the smoke is bound by hemoglobin and hence reduces blood oxygen carrying capacity. Research shows that smoking is a dominant predictor of airway obstruction. Pulmonary function test (PFT) values should be measured to determine airway obstruction. PFTsare widely used to understand and rate the abnormalities in respiratory system functions. The air entering and leaving the lungs should be able to move fast enough and play a decisive role in physical capacity.Air velocity depends on theairway resistanceof chest and lung tissues, affecting dynamic measurements (10, 11).

1) FVC (forced vital capacity) is the maximum amount of air exhaledafter a maximum inhalation.There is little or no difference between VC and FVC in normal subjects.
2) FEV1 (forced expiratory volume in one second) is the maximum amount of air expelled during the first-second after a maximum inhalation.This is the most commonly used value to measure lung function. Exercise-induced bronchoconstriction (EIB) diagnosis requires a ≥ 10% fall in FEV1 after exercise.
3) FEV1/FVC ratio is the ratio of the forced expiratory volume in the first second to the forced vital capacity of the lungs. It is normally 80–90% and goes below 70% in the case of obstructive pulmonary diseases.

The aim of this study was to determine the effect of royal jelly on the pulmonary functions of sedentary male smokers aged 25-30 years.

Material and Method

The study was approved by the ethics committee of the university. The study sample consisted of 83 sedentary single male participants aged 25-30 years without any health problems between January and February 2019. Participants were asked whetherthey had any lung disease in the past or now, whether they smoked and how many cigarettes they smoked per day, how long they had been smoking, and whether they were performing physical activity or not. The exclusion criteria were (1) being diagnosed with a disease affecting respiratory functions, (2) receiving bronchodilator therapy, (3) having a neuromuscular and/or cardiopulmonary disease, (4) having undergone abdominal and thoracic surgery, (5) using alcohol and drugs, and (6) refusing to participate in the study. The smoker groups consisted of those who had been smoking for at least 5 years and 10 to 20 cigarettes per day. The non-smoker groups consisted of those who had never smoked before. Participants were randomly assigned to four groups: smoker experimental (Group I: 22), non-smoker experimental (Group II: 21), smoker control (Group III: 20), and non-smoker control (Group IV: 20). Anthropometric measurements were performed before intervention. Body weight was recorded in light clothing and height without shoes. Body mass index (BMI) was calculated by dividing weight (Kg) by the square of height (m). The experimental groups consumed 1000 mg/day pure royal jelly in glass vials between 08.00 and 10.00 am for 21 days. The control groups consumed a placebo liquid in glass vials between 08.00 and 10.00 am for 21 days. The medications were stored in boxes labeled as A and B. The participants were blinded to the allocation throughout the study period and were educated to follow a healthy lifestyle. Participants were instructed not to engage in any exercise or activities requiring physical strength for 21 days. Daily dietary intake data were evaluated at baseline and at the end of the study by 2 days; 1 in the week day 1 in the weekend days by a dietician blinded to the study. They were followed up every week to check the side effects if any and for the compliance. Pre- and post- PFTs were performed using spirometry. VC (L), FVC (L), FEV1 (1), and FEV1/FVC (%) were calculated.

During the measurements, participants were seated in an upright position on a fixed chair, and their nostrils were occluded with a nose clip to prevent them from breathing through their nose. They were asked to inhale and exhale through their mouth three times followed by a maximum inspiration and then maximum expiration. The best value was recorded after three consecutive repetitions. The PFTs were performed by another researcher blinded to the study protocol.

Statistical Analysis

Scale parameters were described by means and standard deviations. Normality of parameters were tested with Kolmogorov Smirnov Test. One Way ANOVA test was used for normally distributed parameters, and Kruskal Wallis Test was used for non-normal distributed parameters. Mann Whitney U test was used for post hoc test of nonparametric differences. All analysis were performed at SPSS 17.0 for windows at 95% confidence interval.

Results

Of participants, 42 were smokers (at least five years and 10-20 cigarettes per day) while the remaining 41 were non-smokers. All the participants were male, single and all of them have academic educational status. In the study flow diagram; the randomization and the loss to follow up are presented (Fig1).

In the study period no participants reported any side effects.

Table 1 shows the groups' demographic data, indicating no statistically significant difference in age, BMI, or in daily dietary intake between the groups ($p > 0.05$).When the pretest and post test results (PFTs) were examined in terms of lung function parameters such as VC, FVC, FEV_1, it was found that the measured values improved significantly in Group I and Group II (p: 0.000) Table 2

Pretest results of Group I were; 2.31 ± 0.08 L for VC, 2.34 ± 0.08L for FVC, 1.76 ± 0.05 for FEV_1 whereas the improved results were found as 2.41 ± 0.19 L, 2.43 ± 0.21L, and 1.76 ± 0.05 as shown in Table 3.

The pretest results were 2.83 ± 0.07 L for VC, 2.71 ± 0.04L for FVC, 2.18 ± 0.17 for FEV_1 for Group II whereas improved results after royal jelly were found

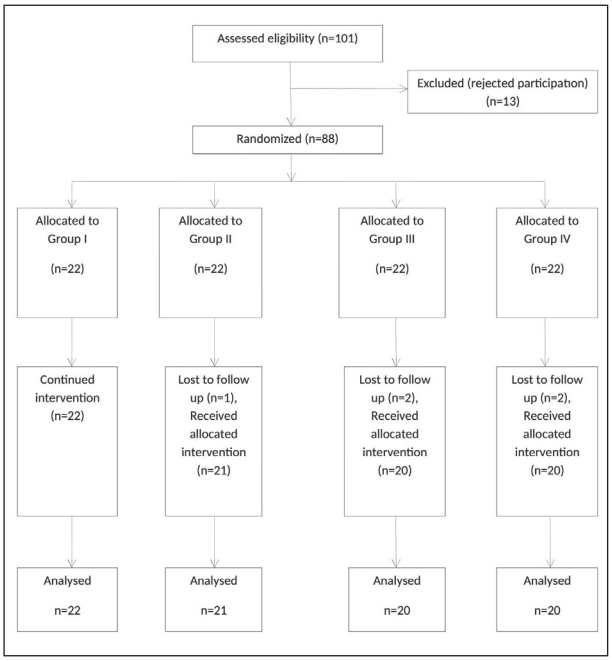

Figure 1: The flow Diagram

Table 1. Demographic parameters of the groups

Pretest, Mean±SD	Group I (n=22)	Group II (n=21)	Group III (n=20)	Group IV (n=20)	P value
Age	27,27±1,64	26,62±1,28	27,20±1,67	26,60±1,35	0.369[b]
BMI	23,73±1,49	23,71±1,71	23,55±1,70	23,20±1,58	0.702[b]
Energy	2328,77±22,25	2324,10±22,23	2326,50±24,38	2325,60±25,42	0.872[b]
Carbonhydrate	243,23±8,28	242,81±6,07	242,05±7,78	243,25±8,36	0.955[a]
Protein	66,82±1,65	67,19±1,78	66,95±1,73	67,15±1,98	0.894[b]
Total fat	115,73±1,86	115,71±1,93	115,45±2,06	115,90±1,71	0.934[b]

a. One Way ANOVA Test, b. Kruskal Wallis H Test, SD: Standard Deviation. BMI: Body Mass Index. P value < 0.05 is considered statistically significant.

as 2.86 ± 0.05L for VC, 2.78 ± 0.09 L for FVC, and 2.25 ± 0.27 for $FEV_{1.}$ respectively.

In other words, Royal Jelly reduced the difference between the initial pulmonary function capacities of smokers and nonsmokers.

Table 4 presents the pretest results of PFT.The main comparison was made between the smokers and nonsmokers. There was no statistically significant difference in pretest measured VC, FVC, and FEV1 values between Group II and Group IV and Group I and Group III (p >0.05).

There was no statistically significant difference in posttest measured VC, FVC, and FEV_1 values between Group I and Group III (p > 0.05). However, Group II had significantly higher FVC value than Group IV (p < 0.05) Table 5.

Figure II shows the pretest FEV1/FVC ratios of the groups. Non-smokers (Groups II and IV) had higher pretest FEV1/FVC ratio than smokers (Groups I and III). Group II had higher pretestFEV1/FVC ratio than Group IV.

Figure III shows the pretest FEV1/FVC ratios of the groupsNon-smokers (Groups II and IV) had higher posttest FEV1/FVC ratio than smokers (Groups I and III). Among non - smokers Group II had higher posttestFEV1/FVC ratio than Group IV whereas Groups I and III had high range.

Discussion

Research shows that cigarette smoking causes respiratory impairment not only at older ages but also at younger ages. Smoking leads to two physiopathological changes in the lungs; (1) the proteolytic destruction of lung parenchyma and emphysema, which is abnormal

Table 2. Pre-test PFT results of the groups

Pretest, Mean±SD	Group I (n=22)	Group II (n=21)	Group III (n=20)	Group IV (n=20)	P value
VC	2.31±0.08	2.83±0.07	2.29±0.07	2.84±0.07	0.000[b]
FVC	2.34±0.08	2.71±0.04	2.32±0.08	2.71±0.03	0.000[b]
FEV_1	1.76±0.05	2.18±0.17	1.74±0.05	2.14±0.05	0.000[b]

a. One Way ANOVA Test, b. Kruskal Wallis H Test, SD: Standard Deviation.

Table -3: Post-test results of the groups

Final, Mean±SD	Group I (n=22)	Group II (n=21)	Group III (n=20)	Group IV (n=20)	p
VC	2.41±0.19	2.86±0.05	2.31±0.07	2.83±0.07	0.000[b]
FVC	2.43±0.21	2.78±0.09	2.34±0.10	2.72±0.04	0.000[b]
FEV_1	1.86±0.19	2.25±0.27	1.77±0.06	2.13±0.08	0.000[b]

a. One Way ANOVA Test, b. Kruskal Wallis H Test, SD: Standard Deviation. VC: Vital capacity, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second. P value < 0.05 is considered statistically significant

Table 4. Pretest Comparison of the groups

Pre-test , p values	VC	FVC	FEV1	FEV1/FVC
Group I- Group II	0.000	0.000	0.000	0.000
Group I- Group III	0.399	0.472	0.367	0.658
Group I- Group IV	0.000	0.000	0.000	0.000
Group II- Group III	0.000	0.000	0.000	0.000
Group II-Group IV	0.606	0.679	0.548	0.712
Group III- Group IV	0.000	0.000	0.000	0.000

VC: Vital capacity, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second.

Table 5. Posttest Comparison of the groups

Post-test, p values	VC	FVC	FEV1	FEV1/FVC
Group I- Group II	0.000	0.000	0.000	0.171
Group I - Group III	0.180	0.323	0.253	0.867
Group I - Group IV	0.000	0.000	0.000	0.068
Group II - Group III	0.000	0.000	0.000	0.084
Group II - Group IV	0.197	0.048	0.260	0.894
Group III- Group IV	0.000	0.000	0.000	0.005

VC: Vital capacity, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second.

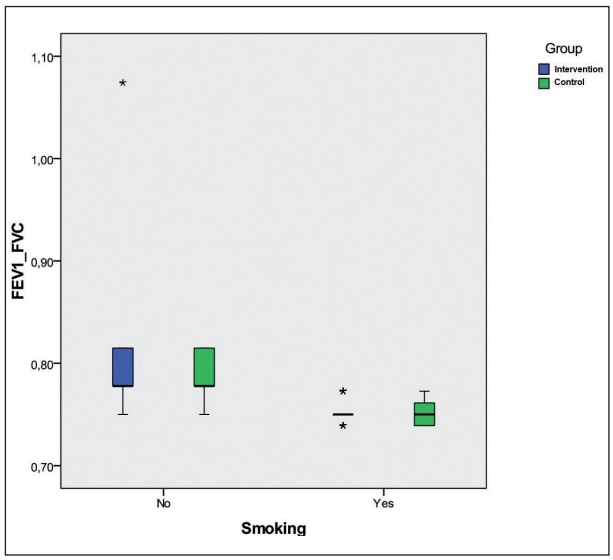

Figure 2: Pretest values of FEV_1/FVC

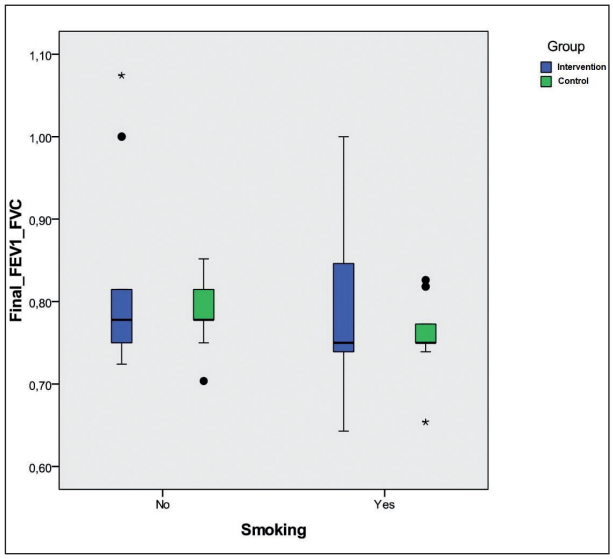

Figure 3: Posttest values of FEV_1/FVC

permanent enlargement of air spaces, and chronic obstructive lung damage and (2) inflammatory constriction of peripheral airways characterized by excessive edema, mucus release and peripheral airway fibrosis. Smoking increases airway resistance and causes prolonged expiration (12, 13). Free radicals increase during chronic inflammation, and the balance between oxidant and antioxidant is adversely affected, resulting in oxidative stress. Smokers have low blood antioxidant capacity. This may not only be due to oxidative stress, but also because it circulates, and therefore, has a systemic effect. Smoking is associated with a reduction in erythrocyte glutathione peroxidase activity, serum antioxidant activity, and plasma ascorbic acid, vitamin E, B carotene, uric acid and selenium levels. There is an increase in the amount of superoxide produced by neutrophils in peripheral blood and a decrease in total antioxidant capacity, especially during the attack and exacerbation episodes of COPD and asthma (14-16).

The harmful effects of smoking on the respiratory system emerge at later ages and is directly proportional to pack-year. Our participants were young and had low pack-year and therefore had normal PFT values. It is known that PFT cannot be used to detect early changes in the small airways, which is supported by some studies. Karimi et al. (17) reported that the prevalence of asymptomatic people with normal PFT values was high among smokers and that early changes in the small airways could be detected by assessing the levels of air trapping in the lungs using computed tomography (CT).

Present analysis demonstrates that there is a positive correlation between royal jelly consumption and lung functions. In vitro studies show that 10H2DA,10-HDAA, and SEA fatty acids in royal jelly reduce the release of nitric oxide, IL 10 and TNF alpha (dose-dependent major inflammatory mediators) and that C, D, A, and E vitamins in it protect lung tissue from harmful oxidative damage. AEOL150 was intratracheally administered 6 hours a day, 3 days a week to rats exposed to filtered air (control group) or cigarette smoke (experimental group) to test whether cigarette-induced inflammation would be reduced by a catalytic antioxidant. The number of cells in the bronchoalveolar lavage of the experimental group rats was significantly reduced. A significant reduction was observed in necrophils and lymphocytes in two days and in macrophages and lymphocytes in eight weeks. At 8 weeks, squamous cell metaplasia was 12% and 2% of the total airway epithelial area in the control and experimental rats, respectively (18).

Antioxidants protect tissues from harmful oxidative damage. Diet is the most important source of antioxidants. The combined activity of dietary antioxidants is probably superior to the individual effect of each antioxidant drug, supporting the hypothesis that royal jelly shows strong antioxidant properties due to the additive effect of its antioxidants (19, 8).

Vitamin C, which is found in tissues and liquids with high potential for free radical production, contributes to antioxidant defense by primarily removing peroxyl and oxygen radicals. One of the mechanisms explaining the protective effects of vitamin C on lung function is as follows: Vitamin C is an important antioxidant in the liquid that covers the surface of the airways. Proteases and antiproteases in that fluid protect the epithelial and immune cells from oxidant attack. Low vitamin C content affects the activity of pulmonary antioxidant defense systems negatively. Royal jelly is a rich source of vitamin C and therefore an important bioactive compound. Vitamin C protects the body from smoke-induced airway inflammation and lung damage and from oxidant air pollutants such as ozone and nitrogen dioxide and also slows down the rate of lung function (FEV1) decline in adults. It has recently been reported that vitamins A and E also slow down the rate of decline in FEV1 and protect respiratory functions in smokers. Royal jelly is rich in vitamins A and E (20-22).

Our literature review showed that there are many studies reporting positive effects of royal jelly on the lungs.El Aidy et al. (23) found that royal jelly and propolis had a positive anti-inflammatory effect on allergic asthma and pulmonary fibrosis in albino rats.Arajua et al. (24) also showed that 1 gram/kg/day royal jellyled to a decrease in the number of Th1-mediated cells and an increase in the number of Th2-mediated cells in the peripheral blood and lungs in people with asthma. Studies argue that royal jelly does that by scavenging free radicals.

Zargar et al. (25) investigated the effect of royal jelly on pulmonary fibrosis induced by bleomycin. They reported that 50-100 mg/kg royal jelly acted as a protective mechanism in bronchoalveolar lavage samples by reducing TGF-β, TNF-α cytokines, and chemotaxis of inflammatory cells and by increasing INF-γ, an antifibrotic cytokine. They also showed histopathologically that royal jelly provided macroscopic improvement.

TNF-α has both inflammatory and fibrogenic properties and is responsible for the development of airway obstruction, inflammation and pulmonary fibrosis. Intracellular studies have shown that MRJP3, a major protein in royal jelly, reduces TNF-α production. IFN-γ prevents fibroblast activation. In vitro studies have shown that IFN-γ has an inhibitory effect on TGF-β signaling pathways. Zargar (25) showed that TGF-β level decreased in royal jelly consumers.

Kamiya et al. (26) conducted an intracellular study of the proapoptoticactivities of royal jelly and reported that HPO-DAEE, a fatty acid of royal jelly, induced apoptosis of A549 cells.They argued that intracellular ROS activated by HPO-DAEE played a role in the destruction of cancer cells. Further research is warranted detailing the chemical structure and clinical application of HPO-DAEE in royal jelly.

In conclusion, proteins, proapoptoticfatty acids, vitamins, and numerous antioxidants in royal jelly can prevent smoking-induced airway obstruction and fibrosis in the early period, and PFTs can yield positive results before there arises a shift in the balance between oxidants and antioxidants in favor of oxidants.

The strength of our clinical trial is randomized and controlled design without inter individual differences however has two main limitations; (1) the sample consisted only of young male participants and (2) smoking participants had a low pack-year history in a short intervention time. Further studies with larger sample sizes with different dosages and durations are needed to provide more evidence regarding the positive effects of royal jelly on pulmonary function.

Conclusion

Royal Jelly is associated with the improvement in lung function even in young smokers with intact oxidant/antioxidant balance and a low pack-year smoking history, however, it is misleading.

Finally, Royal jelly at moderate concentrations has come into promising interest with many health benefits in medicine. Future in vitro trials on respiratory physiology are needed.

Author Contribution

Concept – ETK; MÖ Design – ETK; Supervision – ZP; Materials – AMT; Data collection and/or processing – AMT; ZP Analysis and/or interpretation – MÖ; LitErature review – ETK; ZP Writing – ETK; Critical review – ETK.

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