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To cite this article: Bogdan Pajovic, Nemanja Radojevic, Antonio Dimitrovski, Savo Tomovic & Marko Vukovic (2016) The therapeutic potential of royal jelly in benign prostatic hyperplasia. Comparison with contemporary literature, *The Aging Male*, 19:3, 192-196, DOI: [10.3109/13685538.2016.1169400](https://doi.org/10.3109/13685538.2016.1169400)

To link to this article: <https://doi.org/10.3109/13685538.2016.1169400>



Published online: 05 Apr 2016.



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ORIGINAL ARTICLE

The therapeutic potential of royal jelly in benign prostatic hyperplasia. Comparison with contemporary literature

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Abstract

The aim of this study is to establish the scientific benefit of royal jelly (RJ) on prostatic-specific antigen (PSA), post-void residual (PVR) volume and International Prostate Symptom Score (IPSS) in benign prostatic hyperplasia. For the study, a group of 40 men were administered 38 mg of RJ over a period of three months, their PSA values, prostate volumes and the volumes of their transitory prostate zones, PVR and IPPS values were measured at the end of the first month, and at the end of the third month. The results of this study confirm the potential of RJ in reducing PSA scores and improving IPSS values. Since the use of RJ did not lead to any significant reduction in PVR, prostate volume, or to any involution of the transitory zone, it appears that it may only affect the blood marker of prostatic hyperplasia and to improve quality-of-life (QoL) in those patients. Overall, in comparison to phytotherapy and conventional therapy, RJ had similar positive effects on QoL in patients with BPH, however it exhibited markedly better effects on reducing PSA levels in blood. The therapeutical use of RJ exhibited no side effects.

Introduction

Benign prostatic hyperplasia (BPH) is the result of hyperplasia of the prostatic transitional cell zone, which excretes elevated levels of prostate-specific antigen (PSA), and is very common in men older than 50 years. The main symptoms of BPH are difficult and frequent urination, particularly at night and in severe cases a complete inability to urinate. Patients with BPH exhibit a high PSA level in the blood serum, which is a stronger predictor of prostate growth than prostate volume [1]. In addition, PSA also predicts the changes in symptoms, quality-of-life (QoL), and urinary maximum flow rate (Qmax) [2]. Also, a high prevalence of symptomatic hypogonadism has been observed in populations of aging men with BPH and lower urinary tract symptoms (LUTS) [3]. A validated symptom score questionnaire with questions should be used for the routine assessment of LUTS in all BPH patients as well as measurement of post-void residual volume (PVR) [4]. The International Prostate Symptom Score (IPSS) is an 8-item questionnaire, consisting of seven symptomatic questions and one QoL question [5].

Keywords

Benign prostatic hyperplasia, LUTS, PSA, post-void residual volume, royal jelly

History

Received 27 November 2015

Revised 15 March 2016

Accepted 19 March 2016

Published online 4 April 2016

Commonly used conventional therapies include α 1-blockers and 5 α -reductase inhibitors (5-ARIs). However, none of these treatments has a significant influence on PSA values [3] and may have serious side effects [6–10]. Phytotherapy, either as a monotherapy or in conjunction with conventional pharmaceutical treatments is becoming increasingly popular worldwide. The most widely used phytotherapeutic agent is saw palmetto (*Serenoa repens*) [11], which is well known for positive impact on LUTS. Some studies, however, indicate limitations of saw palmetto with regard to urinary flow measurements and prostate size [12] and LUTS [13], which are the most important problems for patients. Due to various extraction techniques and compositions of various products the data are controversial and, no BPH guidelines recommend plant extracts for initial therapy. Considering these facts it seems appropriate to explore the effectiveness of different, if unconventional treatments.

Royal jelly (RJ) is a creamy product from the cephalic glands of young nurse worker bees (*Apis mellifera*) that has been shown to have considerable health effects [14]. It has been proposed that RJ has anti-inflammatory effects due to possible antiradical and antioxidative effects [15]. Already largely used in folk medicine, RJ has been shown to have several pharmacological actions such as antitumor, antiallergic, and antibacterial, but also can influence cell proliferation, immunomodulation, and migration in different cell cultures [16,17]. Considering these facts the effect of RJ on BPH

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deserves investigation. The aim of this pilot study was to investigate the effects of RJ on PSA values and on QoL of patients with BPH, using assessment of IPPS and PVR and to compare our results with present literature in regard to conventional and alternative medications, especially saw palmetto extract.

Methods

Over a period of two years, 40 men who had been *de novo* diagnosed with BPH accompanied by elevated PSA were studied. The average age of the patients was 68.5 years of age (SD = 10.4, min = 56, max = 79). The inclusion criteria followed for the study were total PSA > 5, patients who had not undergone any previous treatment for BPH, patients who did not exhibit complete urinary retention and patients with moderate or severe symptom scores on IPPS symptom score. Patients with IPSS scores between 0–7 were considered to have mild symptoms; scores between 8–19 as moderate and severe between 20 and 35 [4]. The International Scientific Committee (SCI) and the Union for International Cancer Control (UICC, previously the International Union Against Cancer), recommend the use of only a single question to assess the QoL. The answers to this question range from “delighted” to “terrible” or 0–6. Exclusion criteria for the study consisted of those patients who met the criteria for bacterial prostatitis or chronic prostatic pain syndrome, those who had previous urinary tract infection(s) documented within the previous year, patients with neurological dysfunction and those who had previously exhibited bee venom allergies. Patients who met the inclusion criteria were advised to take the RJ as a therapy of first choice, without using any other medications. We intended to form a placebo control group, but since RJ has a distinctive taste and smell, it proved too difficult, at this stage of research, to formulate a form of the RJ medium which could be used as a placebo, or to remove the taste and smell of RJ without affecting its active components. The single daily dose of 38 mg [18] fresh frozen RJ was taken orally over the course of three months. All patients were supplied with jelly from the same manufacturer (Bee farm JTM, Duke butter 30, Uzice, Serbia). Samples of blood for PSA analysis were taken, before conducting ultrasound examinations. Serum total PSA was measured in a central laboratory using the ARCHITECT i2000, Immunoassay System (Abbott Diagnostic, Abbott Park, IL). The patients’ PSA was initially measured before commencing with the RJ treatment (PSA₀), after one month (PSA_{1M}), and once again after three months (PSA_{3M}). Their PSA values are displayed in tables in ng/mL. The transrectal ultrasound prostate volume was also measured (V), as along with the volume of transitory zone (T), before commencing with the treatment (V₀; T₀), after one month (V_{1M}; T_{1M}), and once again after three months (V_{3M}; T_{3M}). These volume values are measured in mL. IPPS total score and QoL score were first documented before commencing with the RJ treatment (IPPS₀; QoL₀), after one month (IPPS_{1M}; QoL_{1M}) and again after three months (IPPS_{3M}; QoL_{3M}). The same pattern was used for PVR assessment (PVR₀, PVR_{1M}, PVR_{3M}) for which values are measured in mL. Transabdominal ultrasound was used to determine the PVR value. The Agency for Healthcare

Policy and Research (AHCPR) states that, in general, a PVR of less than 50 mL represents adequate emptying and a PVR of greater than 200 mL represents inadequate emptying [19].

Patients were assessed according to European Association of Urology (EAU) guidelines [4], using the IPSS questionnaire at the beginning of the therapy, as well as one and three months later.

- The primary criterion for response was scoring 2 or less (“delighted-to-mostly satisfied”) on the IPSS QoL item [20].
- The secondary criterion for response was greater than 50% reduction in total IPSS score [20,21].

We have analyzed whether parameters were normally distributed using χ^2 test, $\alpha = 0.05$. For normally distributed data, we used one-way ANOVA testing. The Kruskal–Wallis test was used for determination of values that were not normally distributed, as well as for the data measured on an ordinal scale. A post-hoc Conover test followed the Kruskal–Wallis test, to determine differences between each group pairs.

Results

According to χ^2 test, the PVR, V, and T parameters are normally distributed, while PSA is not. Descriptive statistics (mean \pm SD) for the parameters are given in Table 1. There were no statistically significant differences between group means for the parameters V, T, and PVR as determined by one-way ANOVA. A Kruskal–Wallis test showed that there was a statistically significant difference in PSA between the different time periods, $\chi^2(2) = 61.40$; Table 1 showed that oral administration of RJ lowered the PSA value from 12.26 ± 6.59 ng/mL before treatment to 4.58 ± 1.67 ng/mL three months after treatment start. Using a post-hoc test after Conover, we determined that PSA is statistically significantly different between each group pairs.

A Kruskal–Wallis test also showed that there was a statistically significant difference in QoL and IPSS between the different time periods. Using post-hoc test after Conover, we determined that QoL, as well as IPSS, are significantly different between each group pairs. We present descriptive statistics (median \pm IRQ) for the following parameters in Table 2.

Using primary criteria, 22 patients (55%) responded positively after one month of treatment, while 33 patients (82.5%) had a positive response after three months. Using secondary criteria, 10 patients (40%) reported a positive result after one month, whereas 21 patients (52.5%) responded

Table 1. Descriptive statistics for the changes of PSA, V, T, and PVR during observation period.

		PSA	V	T	PVR
Time zero	Mean	12.26	66.75	48.70	50.38
	SD	6.59	14.24	13.31	11.62
One month	Mean	6.26*	65.05	46.63	47.30
	SD	3.94	15.23	13.77	11.29
Three months	Mean	4.58*	62.90	45.93	47.10
	SD	1.67	14.87	13.72	10.63

Asterisk (*) represents statistically significant difference compared with initial values among corresponding groups.

Table 2. Descriptive statistics for the changes of QoL and IPSS during observation period.

		QoL	IPSS
Time zero	Median	4	23.5
	IRQ	2	11.5
One month	Median	2*	14.5*
	IRQ	2	9.25
Three months	Median	2*	12*
	IRQ	1	7.25

Asterisk (*) represents statistically significant difference compared with initial values among corresponding groups.

positively after three months of treatment. None of the patients exhibited adverse effects to therapy.

Discussion

Our study revealed that RJ had a significantly positive effect on QoL and other items of IPSS, progressing from the first till the end of the third month of therapy. However, there were no significant differences with regard to prostate volume or PVR. When comparing studies of the effects of phytotherapy (especially *Serenoa repens*) on LUTS and PVR in patients with BPH, we found many inconsistencies. Wehrberger et al. [22] suggest a positive effect of extracts (saw palmetto, β -sitosterol, rye grass) on LUTS, PVR, and urinary flow rate. The positive influence of *Serenoa repens* on LUTS and QoL in patients with BPH was also reported by Sinescu et al. [23], conversely major Cochrane reviews [13,24] indicate that *Serenoa repens* did not improve symptoms of LUTS nor prostate volume when compared to placebo, which is, in regard to decline of prostate volume, similar to our results, although, our study lacked control or placebo groups. Conventional treatments show significant reduction in IPSS scores and improvement in QoL for patients, but still have a wide range of adverse effects [4]. α 1-blockers typically reduce IPSS [25,26], but do not affect prostate size [9,27]. Similar improvements are obtained by patients receiving 5-ARIs [8]. As a result, many authors have evaluated combinations of phytotherapy and conventional therapies in order to minimize side effects and improve overall results.

In trials *Serenoa repens* has shown similar improvements in IPSS when compared to finasterid (5-ARIs) and tamsulosin (α 1-blocker), this may be interpreted to indicated equivalency between treatments [12,28,29]. A study made by Ryu et al. [28] has also shown that combination treatment of *Serenoa repens* and tamsulosin was more effective than monotherapy with tamsulosin in reducing storage symptoms in BPH patients after 6 months and up to 12 months of treatment. Morgia et al. [30] claimed that *Serenoa repens* in combination with selenium and leucopen is more effective in treating LUTS symptoms if combined with tamsulosin too, which can lead to conclusion that combinations of phytotherapy and conventional therapy yield better results than monotherapy. Conversely, some studies [31] claim that *Serenoa repens* and tamsulosin are more efficacious as monotherapies and that combination therapy does not provide extra benefit. There are also indications that *Serenoa repens* produces similar improvement in urologic symptoms when compared to finasterid [32], thus due to it's fewer adverse effects,

Serenoa repens represents the preferred modality of treatment. None of those studies have shown positive effects of therapy on PSA values, which is a good predictive value for assessing prostate volume [2,33]. Since prostate volume is a risk factor for acute urinary retention, the ability of PSA to predict prostate growth may be an important factor when considering individual treatment options for BPH [1]. A critically important result of our research was a decline in PSA values after three months treatment with RJ, which has not been achieved with phytotherapy or conventional treatment yet. Nevertheless, none of the measured prostate volume parameters (V and T) among examinees decreased significantly. It seems that lower PSA values after three months might be due to a direct effect of RJ administration on PSA blood levels without reducing the prostate volume. A recent randomized trial [34] has shown no positive effect of saw palmetto on serum PSA, in comparison to placebo, even at relatively high doses. However, our study was not placebo-controlled, hence this comparison is incomplete. There are no contemporary results confirming positive short time influence of α 1-blockers on PSA values. Another randomized placebo-controlled trial study, however, [9] revealed that three months treatment with alfuzosin does not affect total or transition zone volume of the prostate, which is similar to our results, although our examinees reported significant improvement of symptoms without adverse effects to therapy, a potentially important therapeutical issue of RJ in the future. 5 α ARIs lead to reduction of prostate size and PSA only after 6–12 months of treatment [35], while our study showed significant PSA reduction only after three months of treatment with RJ.

RJ is already known as strong antioxidant and anti-inflammatory agent *in vitro* [36]. Also, it has been demonstrated that RJ possesses numerous functional properties such as antibacterial, anti-inflammatory, and metabolic activity [37,38], but there were no contemporary studies showing its potential effect on prostate nor QoL in patients with prostate disease, especially BPH. It is clearly evident that RJ makes significant decline in LUTS and PSA values, in a short period of time, although the exact mechanism is not known yet, since V and T did not improve significantly. Moreover, it can mask the laboratory findings of PSA, while the actual cause of the problem (glandular hyperplasia) remains unaffected. This could be particularly damaging for the early diagnosis of prostate cancer, where the value of PSA is a useful predictor. Future studies may show the effect of RJ on PSA values in patients with normal prostates. Also studies should include various doses and concentrations of RJ to determine the effect on the benefits produced by, increase the benefits of RJ, even on prostate volume. Thus, we need to make more comprehensive, randomized placebo studies in the future to confirm results of our pilot study and before we can come to any final conclusions on the true potential of RJ.

Conclusion

Overall, when compared to phytotherapy and conventional therapy, RJ has similar positive effects in QoL and symptoms of LUTS in patients with BPH, but clearly better effect on reducing PSA levels in blood. Therapeutical effects were seen rapidly and exhibited no side effects. However, since RJ

affects PSA values it is essential to rule out the presence of prostate cancer before treatment to avoid the risk of masking results of PSA screening for cancer. The limitations of our study include small sample group, the absence of a control group treated with placebo, and the absence of a follow up period post-treatment. Further research in a more comprehensive study, focused on the true potential of RJ on prostatic tissue, may yield revolutionary results.

Declaration of interest

No part of this paper has been presented, published, or submitted for publication elsewhere in this or in any other language.

This clinical study was conducted in accordance with the principles laid down in the WMA Declaration of Helsinki along with the strict respect of patient's rights and clinical study protocol. Patient confidentiality and data security is guaranteed.

Authors did not have any support in funding of the paper. The authors of this paper hereby declare that have not received nor shall receive any financial benefits from publishing the paper, neither have they received any financial incentive from a third party. We, the author and co-authors, hereby solemnly declare that we are not in any situation which could give rise to a conflict of interest.

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