

# Date Palm Pollen versus Pentoxifylline on Improvement of Sperm Parameters in Idiopathic Male Infertility

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## Research

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# Abstract

**Background:** Idiopathic male infertility (IMI) affects nearly 30 to 45% of men in their optimal reproductive age. In this regard, there are no evidence-based medications prescribed empirically to treat IMI. However, applying traditional medicine for the treatment of male infertility has attracted more attention in recent years. In the current study, the effects of date palm pollen (DPP) on sperm parameters in patients with idiopathic infertility were evaluated and compared to pentoxifylline (PTX).

**Materials and methods:** This study was performed on 80 adult male individuals (20-35 years old) who had oligozoospermia and/or asthenozoospermia and/or teratozoospermia. Patients received 6g DPP powder or 400 mg PTX tablets daily for three months in two separated groups (each in 40). Various sperm parameters and levels of sex hormones were measured.

**Results:** Compared to the PTX group, results revealed a significant improvement in sperm counts ( $p=0.016$ ), morphology ( $p=0.029$ ), total motility ( $p=0.018$ ), progressive motility ( $p=0.016$ ) and reduction of immotile sperms ( $p=0.014$ ) in patients who received DPP treatment.

**Conclusion** Iranian Traditional Medicine (ITM) strongly recommended DPP as a therapeutic agent to cure IMI through improvement in the functional competence of sperm and semen parameters.

## Introduction

Infertility is a global health issue with a social burden defined as an inability to achieve a pregnancy after one year of regular, unprotected sexual intercourse [1]. Near to 15% of couples suffer from infertility problems during their marital life [2]. According to epidemiological reports, about 20 to 70% of infertility cases are male-associated problems and among them, 30 to 45% are idiopathic with unknown etiology [3–5]. Either in traditional or modern medicine, the quantitative and qualitative decline in semen is the main factors of male infertility [6–8]. To our knowledge, different hormonal medications and nutritional or antioxidants supplements are highly recommended [9–12]. However, the effectiveness of current therapeutic approaches has not been completely proven [13–14]. Although some studies have shown the positive effects of gonadotropins on the semen parameters and fertility rate, the administration of gonadotropins remains a controversial issue [15–16]. Nevertheless, it has been shown that anti-estrogens agents are useful in a small percentage of patients with infertility [17]. In addition, assisted reproductive technologies methods are invasive and expensive and do not necessarily promote satisfactory outcomes [18]. Therefore, it seems that more investigations are desperately required to find more effective medications with fewer side effects. Recently, application of traditional and complementary medicine is globally developed for the management of fertility-related disabilities such as IMI [19]. *Phoenix dactylifera* known as date palm pollen (DPP) is the male reproductive cells of palm flowers known as a natural product that considered a strong stimulant of sexual potency and fertility in ITM [20]. Multiple mechanisms have been suggested for the pharmacological functions of DPP on male reproductive system. Previous studies reported that DPP is a rich source of amino acids as the main constituents, significant amounts of vitamin A, E, C and some types of vitamin B such as B1, B2, and B12, fatty acids, enzymes and minerals such

containing zinc, selenium, iron, molybdenum, cobalt, copper, manganese, and nickel [21–23]. This natural product also contains carotenoids, tannins, saponins, flavonoids, and steroidal compounds such as estrogen, cholesterol, estrone, estradiol, and sterol, and also phenolic components [24, 25]. Based on an in vitro study, the addition of this herbal extract to culture medium could increase sperm motility [26]. Moreover, several animal studies have also explored the pharmacological effects of DPP such as augmentation of sexual function, male fertility, and semen quality in terms of sperm count, motility, and normal morphology [27]. However, few clinical studies are available concerning the effects of DPP on the semen parameters. In present study, we aimed to compare the beneficial effects of DPP with PTX on IMI at least in one of the semen parameters.

## **Materials And Methods**

### **Study design and patient population**

This study is a retrospective, randomized, single-blind, and comparative clinical trial which was conducted on men with idiopathic infertility. The study was performed from April 2015 to January 2018 in Yas Hospital, Tehran, Iran. Eighty adult male subjects, aged between 20 to 35 years old, were selected with inability to conceive after at least one-year unprotected intercourse as well as a defect in sperm count and/or motility and/or morphology according to world health organization (WHO) standards [28]. Patients were examined by an expert urologist carefully in terms of major urogenital disorders listed below:

Cryptorchidism, history of genital trauma, hypospadias, epispadias, gynecomastia, testicular torsion, mumps, sexual infection, evidence of hypogonadotropic hypogonadism, testicular atrophy, varicocele, orchitis, history of exposure to chemicals or radiation, endocrine diseases, chronic liver and kidney diseases, other systemic diseases, genetic disorders, and the history of radiotherapy and chemotherapy, as well as family history of infertility, sexual behaviors and the history of drug use.

### **Measurement of hematologic and hormonal parameters**

For all patients, various biochemical parameters including Complete Blood Count (CBC), Fasting Blood Sugar (FBS), Triglyceride, Cholesterol, Thyroid-Stimulant Hormone, Testosterone, Prolactin, Luteinizing Hormone (LH), and Follicle Stimulating Hormone (FSH) were assessed. Testicles ultrasonography was requested in suspected cases of varicoceles and other urogenital disorders.

### **Inclusion/exclusion criteria**

The associated disorders such as varicocele, history of mumps, chronic liver or kidney disease, endocrine diseases, or other systemic diseases were excluded from the study. Inclusion criteria included men ( $\leq$  35 years old) with idiopathic infertility suffering from oligozoospermia and/or asthenozoospermia and/or teratozoospermia, with at least one year unprotected intercourse, without any drug treatment of infertility in the last three months, absence of any known disease that may be associated with male infertility, and without drug history of sulfasalazine, cyproterone acetate, flutamide, cimetidine, spironolactone

consumption and any medication that affect spermatogenesis. Exclusion criteria included serious drug side effects and dissatisfaction to continue the study.

### **Semen preparation and analysis**

In all patients, semen was provided three days after the patient's last ejaculation by masturbation in the laboratory. Patients were randomly assigned to the control and intervention groups using a randomized block design. Before and after the intervention, semen analysis was performed by a technician in a specialized infertility laboratory of the IVF (*In Vitro* Fertilization) department (Yas hospital, Tehran, Iran). According to the WHO, it is advisable to have at least two semen analyses from these patients [22].

### **Drug preparation and treatment**

In DPP group, patients received 6 g of natural agent powder daily in two separate doses (3 g every 12 h). The Liebermann-Burchard reaction as a colorimetric assay was used for the quantification of total sterols (absorbance at 625 nm). Briefly, 250 ml chloroform was added to 20 g of DPP powder and put in ultrasound for 10 min. Next, the mixture was filtered and dried at reduced pressure. The dried residue was dissolved in 10 ml chloroform. Liebermann-Burchard reagent (1 ml) was added to this solution. The absorbance was measured at 640 nm against chloroform blank. Finally, the total sterol content was calculated as an equivalent of  $\beta$ -sitosterol [29]. The DPP derived from palm groves products in Jahrom, South of Iran and standardized based on total steroids (0.044 mg/g DPP). In the PTX group, patients received 400 mg PTX tablet (Farabi Pharmacy, Isfahan, Iran) once daily. The course of treatment was 90 days in both groups. 30 days after treatment process, semen analysis was performed in all the patients. During treatment, patients did not receive any other drugs that affected the parameters of semen. All patients were monitored monthly for possible drug side effects. Possible drug side effects were recorded and assessed based on the common toxicity criteria table. In this single-blind study the semen analysis was performed by the same technician who was blind regarding the information as well as drugs used by patients. Moreover, during the course of the treatment, patients did not receive other drugs for infertility treatment or any drugs that affect the semen parameters. All patients were monitored monthly between two tests. They were also monitored for possible side effects of the drug and regular consumption of the drug.

### **Statistical analysis**

In this study, the primary outcomes consist of sperm related count, morphology, motility and the volume of semen considered as secondary outcome which are the most important variable in male infertility. Sample size was calculated to compare the mean differences in total motility percentage with 90% statistical power and 0.05 significance level for detecting 15% difference between the two groups; Data were represented as mean and standard error (mean  $\pm$  SE) for numerical variables. Analysis of covariance (ANCOVA) was also used to compare the changes in sperm parameters average between DPP and PTX groups, adjusting for baseline values. *T-test* was used to compare the mean of parameters at baseline. A paired sample *t-test* was used to compare the mean of parameters of pre- and post-treatment in both groups. A *p*-value of less than 0.05 was considered as statistically significant.

## Results

A total of 80 patients was included in both DPP and PTX groups (n= 40). There was no drug complication in either DPP or PTX groups. The demographic and baseline data of both groups are shown in Table 1. There was no statistically significant difference in terms of age, body mass index, infertility duration, smoking and endocrine profiles ( $P>0.05$ ). As shown in Table 2, the comparison was performed between semen parameters during pre- and post-treatment in both groups. The results showed that administration of PTX did not statistically improve any semen parameters. However, administration of DPP improved motility, sperm count, and morphology of semen parameters. It should be noted that DPP has no effect on the volume of semen. Based on our findings (Table 3), there was no statistically significant difference in baseline semen parameters between two groups before treatment. The results demonstrated that the mean of some semen parameters has been improved after DPP treatment in compare with PTX group. Particularly, we showed that there is a significant increase in sperm concentration ( $p = 0.016$ ), total sperm count ( $p = 0.012$ ), and normal morphology ( $p = 0.029$ ) in DPP group in compared with PTX group. In terms of motility profile, there was also a significant recuperation in progressive motility ( $p = 0.016$ ) as well as total motility ( $p = 0.018$ ) in the DPP group. The statistically significant differences were not observed between two groups regarding non-progressive motility ( $P>0.05$ ) while immotile sperms decreased significantly in the DPP group ( $p = 0.014$ ). The volumetric changes were not significant in both groups ( $p = 0.140$ ). Overall, 13 cases of pregnancy occurred in both groups during the four months, in which 8 pregnancies in the DPP group and 5 pregnancies in the PTX group were observed, respectively.

## Discussion

Despite many efforts to identify new interventions of IMI treatment, almost no evidence-based agent has been introduced yet [9, 28]. In this regard, herbal medicine is assumed as a valuable source for identifying and discovering new natural drugs [21, 30, 31]. In this study, the effect of DPP, as male reproductive dust of palm flowers, was compared with a conventional drug, pentoxifylline, for the treatment of IMI. Our results showed that in infertile men with idiopathic oligozoospermia and/or asthenozoospermia and/or teratozoospermia, the daily consumption of 6 g DPP can significantly improve the quality of semen in terms of sperm concentration, total sperm count, normal morphology compared with PTX (400 mg, daily) during three months. Beside the different minerals, DPP also contains various antioxidants such as flavonoids, carotenoids, alkaloids, and tannins which have high efficiency on the male genital system and normal spermatogenesis [25, 32, 33]. The majority of animal experiments have shown the beneficial effect of DPP on the male reproductive system and sexual function as well as increasing the power of fertility and improving sperm count and motility parameters [26, 27]. Faleh and Sawad showed the stimulatory effects of DPP on sperm motility and total sperm count in male rabbits at the doses of 5 and 25 mg/kg after 8 weeks [34]. Another study on healthy male rats indicated that aqueous suspension of this agent at various doses including 30, 60, 120, and 240 mg/kg could be able to increase the sperm count and motility in all the studied groups as well as improved normal morphology in doses of 120 and 240 mg/kg during 35 days [35, 36]. Furthermore, the protective role of DPP has been reported on the genital tract and spermatogenesis against cadmium toxicity in male rats [37]. In line with previous studies, our findings strongly confirm a

significant amplification of sperm quality parameters including sperm count, motility and morphology after DPP administration in patients who suffer from IMI [38–40]. It is worth to note that nutritional deficiencies such as zinc and selenium are one of the risk factors contributing to male idiopathic infertility especially in terms of sperm count and motility [41]. The various nutritious components in DPP have been prepared enriched nutrient environments to improve the quality of semen. Among different macronutrients, amino acids such as arginine used in empirical treatment of male infertility and some sexual hormones such as FSH, LH and estradiol components consider as main constituents of DPP to improve sperm quality and spermatogenesis [9, 22, 42]. Based on results from a recent systematic review, it has been shown that the FSH plays a positive role on spermatogenesis and the improvement of sperm parameters in men with idiopathic infertility as well as increasing sperm concentration and subsequent fertility rate [16]. Additionally, some studies assumed that DPP increases serum and intra-testicular levels of testosterone which is necessary for functional spermatogenesis [23, 37].

## Conclusion

Our findings suggest that DPP can be used as an effective drug for improving semen parameters in men with idiopathic infertility. This study can confirm the effects of DPP on increasing male fertility in IMI subjects. Further studies are recommended to determine the underlying mechanisms and related molecular pathways.

## Abbreviations

ANCOVA, Analysis of covariance; CBC, Complete Blood Count; DPP, Date Palm Pollen; FBS, Fasting Blood Sugar; FSH, Follicle Stimulating Hormone; IMI, Idiopathic Male Infertility; ITM, Iranian Traditional Medicine, LH, Luteinizing Hormone; PTX, Pentoxifylline; WHO, World Health Organization

## Declarations

### Ethics approval and consent to participate

The ethical approval of this study was issued by the Ethics Committee of Tehran University of Medical Sciences (Ethics number: IR.TUMS.REC.1394.146559). This study was also registered in the Iranian Registry of Clinical Trial (IRCTID: IRCT2014111519965N1). Informed consent was filled up by all patients who participated in the current study.

### Consent for publication

Not applicable.

### Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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## Authors' Contributions

MRM and MK designed the study, FAA and MS collected the data, MSY performed data analysis, RR and GP contributed for writing the manuscript.

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## Competing Interest

The authors confirm that this article content has no conflicts of interest.

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## Tables

<b>Table 1.</b> Comparison of the Demographic Characteristic and Sex Hormones Level			
<b>Variable</b>	<b>Pentoxifylline (n=40)</b>	<b>DPP (n=40)</b>	<b>P value</b>
<b>Age (year)</b>	32.12 ± 0.547	32.95 ± 0.448	0.246
<b>BMI (kg m<sup>-2</sup>)</b>	26.10 ± 0.431	26.47 ± 0.538	0.593
<b>Infertility (year)</b>	4.45 ± 0.560	4.10 ± 0.560	0.658
<b>Smokers (%)</b>	16 (40.0)	13 (32.5)	0.485
<b>FSH (IU/mL)</b>	4.67 ± 0.51	4.82 ± 0.41	0.383
<b>LH (IU/mL)</b>	4.95 ± 0.33	5.06 ± 0.48	0.119
<b>Testosterone (IU/mL)</b>	4.22 ± 0.24	4.55 ± 0.25	0.754

**Table 2.** Comparison of semen parameters pre- and post- treatment in both groups (DPP vs. PTX). Values are expressed as mean  $\pm$  SE.

Variable semen Parameters	PTX group (n=40)			DPP group (n=40)		
	Before treatment	After treatment	p <sup>1</sup>	Before treatment	After treatment	p <sup>1</sup>
Volume (ml)	3.03 $\pm$ 0.19	2.67 $\pm$ 0.27	0.297	2.96 $\pm$ 0.22	3.04 $\pm$ 0.24	0.123
Sperm concentration (million/ml)	30.61 $\pm$ 4.01	31.27 $\pm$ 4.49	0.887	28.30 $\pm$ 6.64	47.26 $\pm$ 10.97	0.004
Total sperm count (million)	94.39 $\pm$ 15.27	88.97 $\pm$ 15.77	0.766	69.55 $\pm$ 18.42	125.00 $\pm$ 23.46	<0.001
Normal morphology (%)	8.82 $\pm$ 0.82	9.52 $\pm$ 0.83	0.410	7.85 $\pm$ 1.03	11.40 $\pm$ 1.12	<0.001
Total motility (%)	37.75 $\pm$ 3.87	40.07 $\pm$ 3.68	0.448	30.90 $\pm$ 3.29	46.23 $\pm$ 3.70	<0.001
Progressive motility (%)	3.95 $\pm$ 1.26	4.47 $\pm$ 1.08	0.727	3.20 $\pm$ 0.79	9.01 $\pm$ 1.65	0.001
Non-progressive motility (%)	33.80 $\pm$ 3.47	35.60 $\pm$ 3.21	0.539	28.20 $\pm$ 3.08	37.97 $\pm$ 3.35	0.006
Immotile (%)	62.25 $\pm$ 3.87	59.92 $\pm$ 3.68	0.448	68.60 $\pm$ 3.33	53.01 $\pm$ 3.78	<0.001

DPP: Date Palm Pollen, PTX: Pentoxifylline

1. Paired t-test (p<0.05 was considered as significant.)

<b>Table 3.</b> Comparison of semen parameters in baseline and post treatment phases. Values are expressed as mean $\pm$ SE.						
Variable semen Parameters	Baseline			After Treatment		
	PTX group	DPP group	p <sup>1</sup>	PTX group	DPP group	p <sup>2</sup>
Volume (ml)	3.03 $\pm$ 0.19	2.96 $\pm$ 0.22	0.688	2.67 $\pm$ 0.27	3.04 $\pm$ 0.24	0.140
Sperm concentration (million/ml)	30.61 $\pm$ 4.01	28.30 $\pm$ 6.64	0.429	31.27 $\pm$ 4.49	47.26 $\pm$ 10.97	0.016
Total sperm count (million)	94.39 $\pm$ 15.27	69.55 $\pm$ 18.42	0.666	88.97 $\pm$ 15.77	125.00 $\pm$ 23.46	0.012
Normal morphology (%)	8.82 $\pm$ 0.82	7.85 $\pm$ 1.03	0.126	9.52 $\pm$ 0.83	11.40 $\pm$ 1.12	0.029
Total motility (%)	37.75 $\pm$ 3.87	30.90 $\pm$ 3.29	0.182	40.07 $\pm$ 3.68	46.23 $\pm$ 3.70	0.018
Progressive motility (%)	3.95 $\pm$ 1.26	3.20 $\pm$ 0.79	0.247	4.47 $\pm$ 1.08	9.01 $\pm$ 1.65	0.016
Non-progressive motility (%)	33.80 $\pm$ 3.47	28.20 $\pm$ 3.08	0.256	35.60 $\pm$ 3.21	37.97 $\pm$ 3.35	0.178
Immotile (%)	62.25 $\pm$ 3.87	68.60 $\pm$ 3.33	0.236	59.92 $\pm$ 3.68	53.01 $\pm$ 3.78	0.014
PTX: Pentoxifylline, DPP: Date Palm Pollen, (p<0.05 was considered as significant.)						
1.Independent sample <i>t</i> -test						
2.ANCOVA (analysis of covariance)						

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementary.docx](#)