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Impact of the Persian Medicine Formulation "Dava al-Basal" on Sexual Dysfunction and Testosterone Levels in Men Receiving Methadone Maintenance Therapy: A Randomized Double-Blind Clinical Trial

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ABSTRACT

Men on methadone maintenance treatment (MMT) frequently experience sexual problems, particularly erectile dysfunction. The purpose of this research was to investigate the impact of a traditional Persian Medicine formulation known as "Dava al-basal" on erectile dysfunction and serum testosterone concentrations in males undergoing MMT. In this double-blind, randomized controlled trial, 60 male participants were allocated randomly to two groups. The treatment group was given 20 mL of "Dava al-basal" each day—a syrup made from white onion juice, ginger, and honey—while the control group received a plain syrup for a duration of eight weeks. Assessments were conducted at baseline and at the study's conclusion using the International Index of Erectile Function (IIEF) questionnaire and measurements of total testosterone levels. No notable improvements in IIEF scores were observed in either group after the treatment period ($p > 0.05$). In the treatment group, baseline testosterone levels were 197.67 ± 23.08 ng/dL, rising to 325.23 ± 32.73 ng/dL post-intervention ($p < 0.001$). Conversely, in the control group, levels started at 215.33 ± 28.35 ng/dL and fell to 194.17 ± 32.46 ng/dL ($p = 0.047$). This represented a 64% rise in testosterone in the treatment group versus a 10% decline in the control group, with the intergroup difference being highly significant ($p < 0.001$). The formulation "Dava al-basal" demonstrated promise in elevating testosterone concentrations among men on MMT, though it failed to improve sexual performance. Additional studies involving extended treatment durations and further biochemical markers are suggested to confirm these outcomes.

Keywords: Erectile dysfunction, Methadone, Onions, Persian medicine, Testosterone

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Introduction

Sexual dysfunctions, especially erectile dysfunction, are prevalent in males and can adversely influence psychological well-being and life satisfaction for both the affected individuals and their partners [1, 2]. Erectile dysfunction arises from multiple etiologies. Organically, it can be divided into vascular, hormonal, neurological, structural, and medication-related causes [3, 4]. Opioid consumption is a well-known contributor to male sexual issues, potentially increasing the risk of erectile dysfunction almost twofold [5].

Methadone, a synthetic opioid, is widely employed for managing opioid dependence. Long-term use in the form of methadone maintenance treatment (MMT) is a standard approach [6]. Males on MMT often report sexual impairments affecting areas such as arousal, pleasure, climax, and penile erection [7]. These alterations may involve interference with the hypothalamic-pituitary-gonadal axis, resulting in reduced testosterone production [8]. Investigations have explored herbal remedies for alleviating male sexual dysfunctions [9]. Certain formulations from Persian Medicine have also shown benefits in relevant trials [10, 11].

Traditional medical literature has addressed sexual dysfunctions extensively over centuries, providing detailed categorizations and therapeutic strategies. These include dietary and lifestyle adjustments, physical interventions, and phytotherapeutic compounds [12-14]. "Dava al-basal" is a remedy described in Persian medicinal sources, recommended particularly for male sexual complaints like erectile dysfunction. Its primary components are onion juice and honey, supplemented with herbs including ginger, cinnamon, and long pepper (Piper longum) to boost efficacy [15, 16].

Studies in animal models indicate that onion, a central component, supports male reproductive health. Different preparations—such as juice, extracts, peel, or seeds—have exhibited beneficial impacts on sexuality in males, largely via elevating testosterone [17].

This investigation sought to assess the efficacy of the Persian Medicine remedy "Dava al-basal" in addressing sexual dysfunction and testosterone concentrations in males receiving MMT.

Materials and Methods

Reagents

Chemicals for assessing total phenolic content, such as Folin-Ciocalteu reagent, gallic acid, and sodium carbonate, were obtained from Sigma–Aldrich Chemical Co. (USA).

Botanical materials

White onions (Allium cepa L.), ginger (Zingiber officinale Roscoe), and honey were procured from markets in Tehran, Iran. Botanical authentication was performed, with specimens deposited (voucher Nos. PMP-2215 for onion and PMP-2214 for ginger) in the Herbarium at the School of Pharmacy, Tehran University of Medical Sciences (TUMS), Tehran, Iran.

Formulation of the syrup and placebo

"Dava al-basal" was prepared in the pharmaceutics lab at the Faculty of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran. It consisted of onion juice and honey, incorporated with ginger. The recipe followed historical Persian Medicine references [15, 16]. To produce it, 1 liter of juice was extracted from 2.5 kg of white onions, mixed with 50 g of dried ginger powder, then combined with 2 kg of honey and gently heated for about 50 minutes to reach a Brix value above 80, yielding 1900 mL.

Syrup quality was evaluated via total phenolic content determination. Using the Folin-Ciocalteu assay, 1 mL of syrup was combined with 5 mL diluted Folin-Ciocalteu reagent (1:10 in distilled water). After 5 minutes, 4 mL of 7.5% sodium carbonate was added. The mixture was kept in darkness at room temperature for 30 minutes, and absorbance was measured at 765 nm spectrophotometrically. Phenolic content was calculated as mg gallic acid equivalents (GAE) per 100 mL using a calibration curve [18, 19].

Dosing was based on traditional texts [15], set at 20 mL daily in two 10 mL portions every 12 hours. Component concentrations remained within established safety thresholds, with ginger intake below 4 g daily [20] and onion juice up to 100 mL considered safe [21].

The placebo was a basic sucrose-based syrup per British Pharmacopoeia guidelines [22], colored with dark brown caramel (E-150a, B2) from Magnolia Company (Iran).

Microbial testing complied with United States Pharmacopeia criteria [23]. Both active and placebo syrups were packaged identically and blinded with codes.

Study design

This research was designed as a double-blind, randomized controlled trial carried out at a private outpatient facility specializing in drug addiction treatment and rehabilitation in Tehran, Iran, spanning from June 22, 2023, to January 21, 2024. Eligible patients, identified through psychiatric evaluation at the facility, were randomly allocated to receive either the "Dava al-basal" formulation or a placebo over an eight-week period. Assessments for both groups were performed at baseline and upon completion of the treatment phase.

Inclusion criteria

Participants were required to be males aged 20 to 50 years experiencing erectile dysfunction and having a background of opioid dependence. They needed to be on methadone therapy for addiction management, initiated

at least three months earlier. Furthermore, they had to be either married or in a stable heterosexual partnership, with a psychiatric diagnosis of sexual dysfunction. No specific therapy for sexual issues should have been received in the prior three months, and all were required to give informed consent.

Exclusion criteria

Reasons for exclusion encompassed erectile dysfunction attributable to other underlying health conditions (based on psychiatric assessment), concurrent use of drugs or treatments that could influence sexual performance, alcohol dependence, abuse of additional substances, serious psychiatric or personality disturbances, presence of psychosis, risk of suicide, significant hepatic or renal impairment, known drug allergies, or voluntary withdrawal from participation.

Outcome measures

The investigation utilized both a validated questionnaire and a laboratory marker—serum total testosterone—to assess intervention outcomes at the start and after eight weeks.

The International Index of Erectile Function (IIEF) questionnaire is a standard instrument for evaluating male sexual dysfunction. It comprises 15 items across five domains: (1) erectile function (6 items, scores 1–30); (2) orgasmic function (2 items, scores 1–10); (3) sexual desire (2 items, scores 2–10); (4) intercourse satisfaction (3 items, scores 0–15); and (5) overall satisfaction (2 items, scores 2–10). Originally developed by Rosen *et al*. in 1997 [24], domain scores are derived by summing relevant items, and the total score is the aggregate of all domains, with higher values reflecting superior sexual function.

The IIEF has been extensively applied and validated across languages [25]. In a study by Babazadeh *et al*. examining the Persian adaptation among men with substance dependence, reliability was strong, with Cronbach's alpha coefficients of 0.86 for erectile function, 0.69 for orgasmic function, 0.87 for sexual desire, 0.88 for intercourse satisfaction, and 0.62 for overall satisfaction [26].

Total serum testosterone concentrations were also measured, with the reference normal range defined as 160 to 720 ng/dL.

Randomization and blinding

Random allocation to the treatment or placebo arms was achieved using Microsoft Excel's Random Number Generation add-on to create a non-sequential list of numbers from 1 to 60, subsequently dividing them equally into two groups of 30. This procedure was managed by the study's methodological advisor, keeping clinicians blinded to assignments. Investigators received only the coded sequence from 1 to 60.

Blinding was maintained by dispensing either the active syrup or placebo in identical sealed PET bottles marked solely with codes. Coding followed instructions from the methodological advisor and was handled by a team member. Consequently, the treating physician, outcome assessor, and participants remained unaware of group allocations. Participants were monitored by the investigator every two weeks for adverse effects, and contact details were provided for reporting any concerns.

Sample size

Sample size determination was performed with G*Power software, assuming 80% power and an effect size of 0.8. Accounting for a projected 15% attrition rate, 30 subjects per arm were deemed necessary, corresponding to an effective target of approximately 26 completers per group.

Statistical analysis

Analyses were conducted using SPSS version 27 (SPSS Inc., USA). Normality was tested via the Kolmogorov-Smirnov method. Continuous data were expressed as means ± standard deviations (or standard errors: ±SE), and categorical data as frequencies and percentages. Group comparisons for continuous variables employed independent t-tests or the Mann-Whitney U test as appropriate; categorical variables were compared with the Chi-square test. Correlations among continuous variables were assessed using Pearson's coefficient. Within-group changes from baseline to endpoint were evaluated with the Wilcoxon signed-rank test, while between-group differences utilized the Mann-Whitney U test. Statistical significance was set at $p < 0.05$.

Results and Discussion

Microbial and fungal evaluations of the syrup included assessments of total aerobic microbial count (TAMC) and total yeast and mold count (TYMC). The samples were also screened for Escherichia coli and Salmonella spp., adhering to the criteria specified in the United States Pharmacopeia [23].

The total phenolic content in "Dava al-basal" syrup was measured at 68.3 µg gallic acid equivalents (GAE) per mL. The formulation satisfied all required standards for microbial and fungal contamination.

A total of 60 patients were recruited, with complete retention and no withdrawals, allowing all 60 to be incorporated into the final analysis **(Figure 1).** The study population comprised individuals receiving MMT at a private clinic in southern Tehran. The mandatory in-person visits for methadone administration facilitated rigorous follow-up, which likely accounted for the absence of dropouts.

Participants had an average age of 45.78 ± 7.79 years. Around 90% (54 participants) possessed no more than a high school diploma. The mean daily methadone dose was 81.83 ± 52.25 mg, ranging from 15 mg to 250 mg. The average length of prior methadone therapy was 56.27 ± 33.49 months. Baseline characteristics, including age, educational attainment, methadone dosage, and treatment duration, showed no statistically significant differences between the groups ($p > 0.05$) **(Table 1).**

Table 2 presents the mean scores across the IIEF domains before and after the eight-week treatment period in both arms. No statistically significant changes were detected within either group for any of the five domains or the total IIEF score ($p > 0.05$). Furthermore, between-group comparisons revealed no significant differences in IIEF parameters at baseline or post-intervention ($p > 0.05$).

Baseline serum testosterone concentrations did not differ significantly between the groups ($p > 0.05$). In the "Dava al-basal" arm, a marked rise in testosterone levels was observed relative to baseline ($p < 0.001$), whereas the placebo arm exhibited a notable decline after eight weeks ($p = 0.047$). Post-intervention comparison between the groups demonstrated a highly significant difference in testosterone concentrations ($p < 0.001$) **(Table 3).**

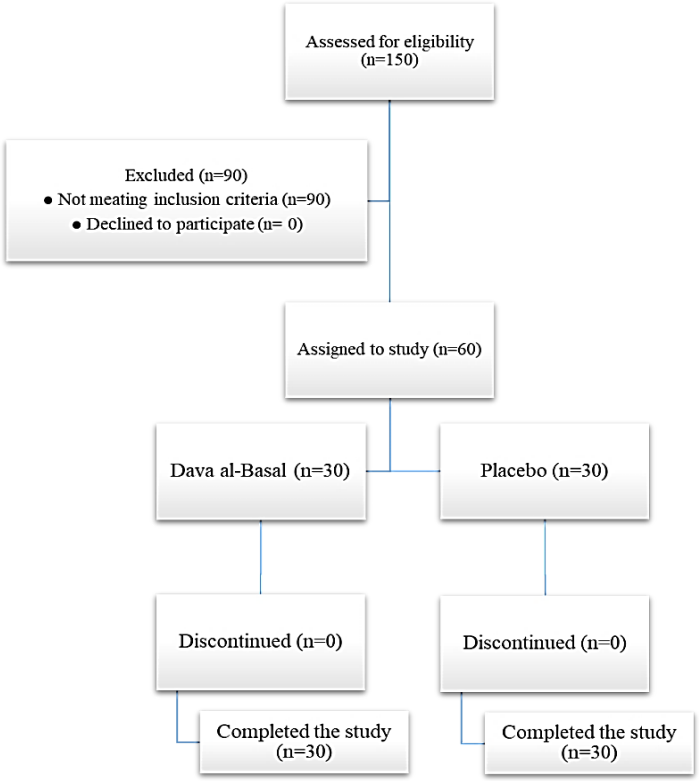

Figure 1. Flowchart of the double blind clinical trial.

Table 1. Characteristics of the Participants

Variable	Dava al-basal (n, %) or mean ± SD	Placebo (n, %) or mean ± SD	P-value
Age (years)	45.37 ± 8.16	46.2 ± 7.51	0.641
Education level			0.089
Illiterate	0	1 (3.3%)	
Elementary school	10 (33.3%)	3 (10%)	

Middle school	10 (33.3%)	10 (33.3%)	
High school	6 (20%)	14 (46.7%)	
Academic	4 (13.2%)	2 (6.6%)	
Methadone dose (mg)	88.83 ± 46.79	79.83 ± 57.93	0.476
Duration of MMT (months)	61 ± 30.35	51.53 ± 36.25	0.185

In this study, administration of the Persian Medicine preparation "Dava al-basal" over an 8-week period led to a 64% increase in testosterone levels, whereas the placebo group exhibited a 10% reduction in testosterone. Nakayama *et al*. (2017) reported that a two-week intake of onion extracts rich in concentrated cysteine sulfoxides significantly elevated salivary testosterone levels in men [27]. Moreover, several animal studies have similarly indicated that onion consumption can enhance testosterone production [17, 28].

Various mechanisms have been proposed to explain the testosterone-boosting effects of onions. These include stimulation of luteinizing hormone (LH) secretion, scavenging of free radicals through enhanced antioxidant defenses within the testes, improvement in insulin sensitivity, increased nitric oxide generation in Leydig cells, and activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) [28]. Additionally, ginger, another ingredient in the syrup, has been reported to raise sex hormone levels, including testosterone, LH, and FSH, across multiple studies. Ginger has also been associated with reductions in oxidative stress and improvements in fertility [29].

Honey has similarly been shown to increase testosterone levels in both animal models and clinical studies [30, 31]. Banihani (2019) suggested that honey may elevate serum testosterone through several pathways, such as stimulating LH production, enhancing Leydig cell viability, protecting these cells from oxidative damage, upregulating StAR gene expression, and inhibiting testicular aromatase activity [32].

Considering that testosterone deficiency is linked to a range of health conditions, including infertility, psychiatric disorders, metabolic syndrome, diabetes, cardiovascular disease, stroke, and fatty liver disease [33–37], the consumption of this traditional formulation may offer potential therapeutic benefits for improving these conditions.

Table 2. Comparison of the five domains of the IIEF questionnaire before and after an eight-week intervention of "Dava al-basal" versus placebo

IIEF Domain	Group	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Mean difference ± SD	Within-group P-value	Between-group P-value
Erectile function	Dava al-basal	15.13 ± 1.44	15.4 ± 1.53	0.27 ± 1.26	0.611	0.667
	Placebo	16.27 ± 1.61	15.83 ± 1.53	0.43 ± 1.51	0.989	
Orgasmic function	Dava al-basal	6 ± 0.53	5.9 ± 0.53	0.1 ± 0.51	0.713	0.714
	Placebo	5.83 ± 0.49	6.1 ± 0.5	0.27 ± 0.47	0.542	
Sexual desire	Dava al-basal	5.37 ± 0.43	5.73 ± 0.43	0.37 ± 0.33	0.269	0.807
	Placebo	5.8 ± 0.39	6.07 ± 0.39	0.27 ± 0.38	0.510	
Intercourse satisfaction	Dava al-basal	6.63 ± 0.65	6.07 ± 0.75	0.57 ± 0.57	0.463	0.346
	Placebo	6.07 ± 0.69	6.37 ± 0.64	0.3 ± 0.52	0.386	
Overall satisfaction	Dava al-basal	5.87 ± 0.52	6.13 ± 0.52	0.27 ± 0.49	0.560	0.875
	Placebo	6.67 ± 0.45	6.97 ± 0.47	0.3 ± 0.43	0.528	
Total score	Dava al-basal	39 ± 3.18	39.23 ± 3.46	0.23 ± 2.66	0.699	0.941
	Placebo	40.63 ± 3.22	41.33 ± 3.21	0.7 ± 2.6	0.558	

Table 3. Comparison of testosterone levels before and after an eight-week intervention with "Dava al-basal" versus placebo

Group	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Mean difference ± SD	Within-group P-value	Between-group P-value

Dava al-basal	197.67 ± 23.08 ng/dL	325.23 ± 32.73 ng/dL	127.57 ± 20.73 ng/dL	<0.001	<0.001
Placebo	215.33 ± 28.35 ng/dL	194.17 ± 32.46 ng/dL	-21.17 ± 32.55 ng/dL	0.047	

Although "Dava al-basal" showed significant efficacy in elevating testosterone levels, participants in the placebo group experienced a 10% reduction in testosterone, which could be related to the adverse effects of methadone maintenance treatment (MMT) on sexual function and testosterone production [7]. The herbal formulation used in this study has not been investigated in prior research. While earlier studies on its individual components, such as onion, ginger, and honey, have suggested potential benefits, the 8-week administration of "Dava al-basal" did not produce observable improvements in the clinical status of patients. Animal studies have indicated that onion intake may enhance sexual behavior, mitigate erectile dysfunction, and improve ejaculation [38, 39]; however, it remains uncertain whether these effects translate to humans. A longer treatment duration may yield more pronounced clinical outcomes, though additional clinical studies are required to explore this possibility.

No adverse events were reported by participants in either the placebo or "Dava al-basal" groups. It is important to note that the study population consisted of individuals on methadone treatment, who may differ from other patient groups; thus, further investigations are needed to comprehensively assess the safety profile of this product. A limitation of this study was its single-center design, and conducting multicenter trials could improve study robustness. Furthermore, the study only measured total testosterone levels; future research should consider evaluating additional laboratory markers, including free testosterone, prolactin, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), to more accurately determine the effect of this Persian Medicine product on sex hormone profiles.

Conclusion

The Persian Medicine-derived product "Dava al-basal" was effective in increasing testosterone levels in men undergoing methadone maintenance therapy compared to placebo. Despite evidence that its components may positively influence male sexual dysfunction, including erectile issues and ejaculation problems [17, 29, 30, 40], our 8-week trial did not show significant improvements in sexual function or erectile status in the intervention group. This lack of effect may be due to the detrimental impact of MMT on sexual function or could indicate that a longer treatment period is necessary to observe potential benefits. Further research, including multicenter clinical trials with extended follow-up, is warranted to validate these findings and confirm the product's efficacy in addressing male erectile dysfunction.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: The research protocol was approved by the ethics board at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1402.181). It was registered in the Iranian clinical trials database under IRCT20230805059047N1. All participants provided informed written consent. The study complied fully with the Helsinki Declaration guidelines.

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