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Effect of Topical Clove (*Syzygium aromaticum* (L.) Merr. & L.M.Perry) Gel on Premature Ejaculation: A Pilot Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract

Premature ejaculation is one of the most common sexual disorders worldwide without a satisfying treatment. In this study, we investigated the efficacy of a topical formulation of clove oil in premature ejaculation patients. Eligible patients were randomly divided into two groups to use either *Syzygium aromaticum* (SA) 1% gel or placebo gel 10 minutes before the intercourse for a period of 8 weeks. Outcome measurement were Premature Ejaculation Diagnostic Tool (PEDT) and International Index of Erectile Function (IIEF) questionnaires in addition to Intravaginal Ejaculation Latency Time (IELT). A total number of 22 (11 patients in each group) participants completed the study. At the end of the intervention, the IELT scores changed from 29.84±18.59 to 97.09±91.86 and 42.51±13.98 to 52.45±32.7 seconds in SA gel and placebo groups, respectively (p-value =0.003). Also, the changes of PEDT scores in the SA gel group (from 14±3.55 to 9.2±4.56) comparing to that of placebo gel group (from 14.63±3.61 to 13.5±3.78) was significantly different (p-value = 0.001). Moreover, results of IIEF questionnaire revealed significant improvement of "Intercourse Satisfaction" in SA gel group (p-value = 0.016). No adverse event was observed. It seems that SA gel could be beneficial in the treatment of premature ejaculation; however, it should be further evaluated in larger studies.

Keywords: Clove; *Eugenia caryophyllata* Thunb; Integrative medicine; Premature ejaculation; Persian medicine; Randomized controlled trial; *Syzygium aromaticum*; Urology; Sexual disorders

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Introduction

Premature ejaculation (PE) is the most common sexual disorder which could negatively affect the fertility and quality of life [1]. Its global prevalence has been estimated to be 30-40% considering that it is an under-reported and under-treated disorder [2]. International Society for Sexual Medicine (ISSM) has defined it as "a male sexual dysfunction characterized by: ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration from the first sexual experience (lifelong premature ejaculation or LPE), OR a clinically significant reduction in latency time, often to about 3 minutes or less (acquired premature ejaculation or APE); the inability to delay ejaculation on all or nearly all vaginal penetrations; negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy" [3]. It has two main types: lifelong (LPE) and acquired (APE) in addition to two subtypes including variable PE and subjective PE [3]. The prevalence of this disorder has a variable range of 4-66% worldwide [4,5]. There are several causes and risk factors for PE including hypersensitivity of glans penis, hyperthyroidism, prostatitis, erectile dysfunction, psychological factors (performance anxiety, wife conflict, and decreased intimacy) [3] as well as physiologic causes (shorter nerve latency time and psychogenic or behaviorally conditioned causes) [6], changes of pituitary or gonadal hormones (oxytocin, prolactin) [7], tense relations between the couples [8], and neurological disorders (such as Multiple Sclerosis) [9]. Furthermore, PE could be the cause of family issues as a result of unpleasant intercourses.

Considering the mentioned etiologies, PE has psychological and/or pharmacological treatments. Psychological treatments consist of an integration of psychodynamic, cognitive, and behavioral psychotherapy approaches in addition to some behavioral techniques such as stop–start or squeeze [3]. Pharmacological therapy includes systemic selective serotonin reuptake inhibitors (such as dapoxetine, paroxetine and off-lable sertraline), phosphodiestrase type 5 inhibitors (like sildenafil) [1], alpha adrenergic blockers as well as topical anesthetics including lidocaine, prilocaine, and benzocaine [3]. However, there is no satisfying response to the treatments [10]. Disregarding the lack of approved treatment, the available medications are associated with sideeffects. For instance, consumption of serotonin reuptake inhibitors (SSRIs) has been accompanied with adverse events including headache, dizziness, anxiety, agitation, insomnia, delayed ejaculation and anejaculation, arousal difficulties, and absent or delayed orgasm [11].

Considering the high prevalence of PE on one hand and lack of efficient medical care to prevent or treat this disorder on the other, it is important to explore novel therapeutic approaches. Traditional and complementary systems of medicine are usually considered as potential sources for finding new medicines based on the historical experiences [12]. Persian medicine (PM) is one of the oldest medical schools rooted in the humoral medicine [13,14]. It could be considered as a potential source for finding novel treatment strategies [15]. Regarding the PE,

it seems that PM scholars have mentioned PE and its treatments in their medical manuscripts for the first time [16]. In PM, clove is known as "*Gharanfol*" (Arabic) or "*Mikhak*" (Persian) having hot and dry nature. It is a tonic agent which is used in different topical and oral dosage forms possessing aphrodisiac properties. The clove oil has been introduced as a topical remedy for sexual disorders and premature ejaculation in PM literature [17,18]. *Syzygium aromaticum* (L.) Merr. & L.M.Perry (*Eugenia caryophyllata* Thunb.) is a member of family Myrtaceae which is commonly known as clove [19]. It is an aromatic flower bud with a vast range of medical and dietary applications since ancient times [20]. German Commission E has approved its use as a safe dental analgesic and a treatment for oropharyngeal inflammations [21]. It should be mentioned that recent findings are also in conformity with using clove for sexual disorders. In an animal study, the effects of clove extract on improving sexual function have been confirmed [22]. Another animal study in diabetic rats confirmed the aphrodisiac activity of clove. In this study, clove essential oil and its main component, eugenol, significantly improved diabetes-induced erectile dysfunction [23]. However, there is no clinical evaluation investigating the efficacy of clove oil in PE. Accordingly, the current pilot study was designed to obtain preliminary clinical evidence about the clove gel efficacy in PE.

Methods

Study design

This study was a pilot randomized, double-blind, placebo controlled clinical trial with 1:1 allocation ratio. It was conducted in Family Health Clinic and Traditional Medicine Clinic of Shahed University, Tehran, Iran from February to November 2016. The study protocol remained unchanged until the end of study.

Ethical issues

The study protocol was approved in the Medical Ethics Committee of Shahed University (ID: shahed.REC.1394.55). It was also registered in the Iranian Registry of Clinical Trials (IRCT) with the ID: IRCT2016013126298N1. Prior to enrollment, participants signed the informed consent form after receiving adequate information about the study.

Plant material

Clove bud was purchased from a traditional herbal shop (*Attari*) in the bazaar of Tehran, Iran. The voucher specimen was deposited at the Herbarium Center of School of Pharmacy, Shahid Beheshti University of Medical Sciences (voucher number: SBMU-8069).

Volatile oil extraction

Thirty grams of the clove bud were powdered and subjected to the hydro-distillation (HD) method for 4 hours using a Clevenger-type apparatus. The achieved essential oil (1% V/W) was separated from the aqueous layer, dried over anhydrous sodium sulfate, and stored at 4 °C until the analysis time.

Preparation of clove oil gel and placebo

To prepare the herbal gel, clove essential oil was mixed with carbopol 934 base gel (1:100). The

placebo gel was made using carbopol gel only. The smell of the scented herbal gel matched by adding 2-phenylethanol from Merck Company (Art. 807006) to placebo gel. Herbal and placebo gels were packed in similar standard aluminum 30 g tubes.

Drug standardization

Qualitative and quantitative analyses of isolated clove essential oil were conducted using Gas Chromatography–Mass Spectrometry (GC-MS) and Gas Chromatography–Flame Ionization Detector (GC-FID) methods. The analytical GC was conducted using an Agilent Technologies 7890A equipped with HP-5 5% Phenyl Methyl siloxan capillary column (30 m × 320 μm i.d., film thickness 0.25 μm; Hewlett-Packard) and FID-300 detector. The column temperature was programmed at 50°C for 2 min, then heated to 280°C with the rate of 10°C/min, and left for 4 min. The injector temperature was 270°, and the carrier gas was N2 with a flow rate of 2 ml/min. To achieve the content of eugenol as the main oil constituent, the peak area from GC-FID chromatogram was compared and discussed using eugenol as standard.

GC-MS was performed via an Agilent 6890 instrument connected to an MS detector, on capillary column BPX5 (30 m × 0.25 μm i.d., film thickness 0.25 μm). The oven temperature was programmed as (50°C for 5 min, then 3°C/min to 240°C, and then 15°C/min to 300°C then left for 3 min). The injection port temperature was 250°C (split ratio: 1/35). The carrier gas was helium with a flow rate of 0.5 ml/min. The detector was Agilent 5973 Mass Spectrometry with the mass range of 40-500 m/z, 70 eV ionization voltageion and 220 °C source temperature.

Retention indices were calculated using retention times of n-alkanes injected after the oil under the same chromatographic conditions. The chemical compounds of clove bud oil were identified comparing the results of the chromatogram and reference retention time (based on Wiley mass spectra library) with those reported in the literature and authentic sample.

Inclusion and exclusion criteria

The inclusion criteria were married men from 18 to 40 years old who are monogamous with Intravaginal Ejaculation Latency Time (IELT) less than one minute (in 2 or more times in each 4 intercourses). Furthermore, they were included if they had LPE after at least 6 months since the beginning of the first sexual intercourse. They should also have had at least one intercourse per week. The score of the Premature Ejaculation Diagnostic Tool (PEDT) questionnaire had to be equal to or more than 9 in addition to stable relationship between the spouses. The patients were excluded if they had erectile dysfunction, sexual desire disorder, substance abuse or alcohol consumption (patient or his wife), diabetes mellitus, thyroid, cardiac, renal, liver as well as severe psychiatric diseases such as bipolar disorder, major depression, and schizophrenia. Furthermore, those who had a history of mental and debilitating diseases such as cancer and did not want to continue the study or failed to obey the instructions were excluded. Other exclusion criteria were using drugs affecting PE within thirty days prior to inter-

vention, pregnancy of wife, using condom as a method of contraception, and skin sensitivity to the clove gel (patient or his wife).

Randomization, blinding and concealment of allocation

Block randomization (block size: 4) was applied using computer generated random numbers. Neither the patients nor the physician could identify the drug and placebo tubes because their color, smell, and shape were similar. The tubes had been specified with their codes.

Intervention

Those patients who met the inclusion criteria were enrolled after signing the informed consent. Thirty-eight participants received either herbal gel (topical clove gel) or placebo (base gel). The study protocol was explained to the patients by the researcher. Their demographic data including age, educational degree, duration of marriage, body mass index and IELT in addition to International Index of Erectile Function (IIEF) and PEDT questionnaires were recorded. The patients had to apply a thin layer (about 0.5 milliliter) of gel rubbing on the glans penis 10 minutes before the intercourse without washing the glans or using condom. The IELT was recorded before and at the end of the study. It was explained to the participants that this index indicates the time period from vaginal penetration to the moment of ejaculation. The researcher's phone number was available to the patients so that they could ask their questions during the study. After 8 weeks from the beginning of the intervention, the patients were visited and the PEDT and IIEF questionnaires were filled again.

Outcome measures

We used PEDT questionnaire, valid Persian translation of IIEF questionnaire, and IELT index for patient assessments. The PEDT questionnaire is a 5-item user-friendly diagnostic tool for PE. The score equal to or more than 11 means that the participant has PE while the score of 9 or 10 indicates probable PE and ≤8 means no PE [24]. Using the IIEF questionnaire, we would know that the patient has not erectile dysfunction. This standard questionnaire has 15 questions which assess erectile function, orgasms, sexual desire, sexual pleasure, and overall satisfaction [25]. The validity and reliability of its Persian translation has been confirmed in a previous study [26]. The IELT index is defined as "the time between the start of vaginal intromission and the start of intravaginal ejaculation" [22] which is frequently used as an assessment measure in PE patients.

Statistical analysis

We used Statistical Package for the Social Sciences (version 20.0) software for data analysis. Qualitative variables were described by number and percentage. Mean and standard deviation were used for presenting quantitative variables. Considering the sample size and non-normal distribution of the quantitative variables, the Mann-Whitney test was applied for comparing the groups. In addition, p-values less than 0.05 were considered as the statistically significant level.

Results

Clove essential oil analysis

GC-MS spectrometry

Table 1 presents the chemical constituents of SA essential oil based on the GC-MS analysis including their retention time, kovats indices, and component percentage. The major components were Eugenol and Eugenol acetate with the percentages of 89.46% and 4.07 %, respectively. The related chromatograph is shown in figure 1.

Table 1. Chemical compositions of *Syzygium aromaticum* essential oil (obtained by hydrodistillation) based on Gas Chromatography–Mass Spectrometry analysis.

No.	Compounds	RT[a]	KI[b]	%
1	Octan	5.83	801	2.53
2	Decane	15.04	1002	0.46
3	Dodecane	25.24	1202	0.14
4	Methyl salicilate	25.55	1208	0.41
5	Chavicol	28.83	1278	0.14
6	Thymol	30.78	1320	0.64
7	Eugenol	33.28	1376	89.46
8	E-Caryophyllene	35.58	1430	1.37
9	α-Humulene	37.14	1476	0.17
10	Eugenol acetate	39.84	1533	4.07
11	Caryophyllene oxide	42.45	1599	0.14
	Total identified			99.53

[a]Retention time; [b]Kovats index

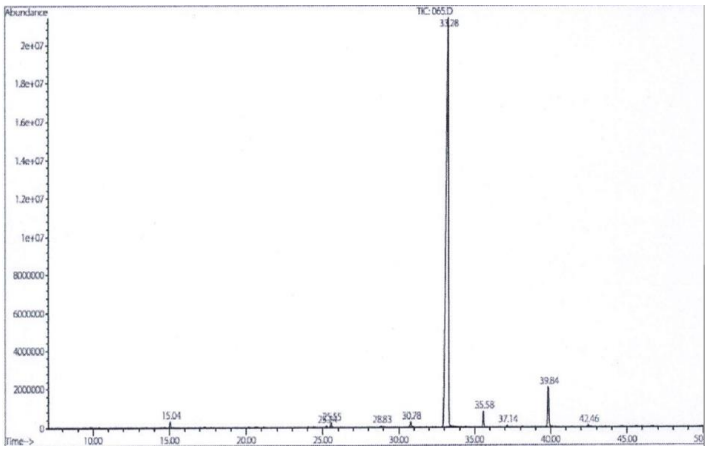

Figure 1. GC-MS chromatogram of clove bud essential oil.

GC spectrometry

Typical gas chromatogram of the GC-FID analysis of clove essential oil and the chromatogram of the GC-FID analysis of eugenol as standard are shown in Figure 2 and 3. Moreover, Figure 4 illustrates the eugenol calibration curve representing concentrations and peak areas for eugenol injection and related equation. The eugenol content in the clove oil was calculated to be 0.007 ± 0.002 mg/ml.

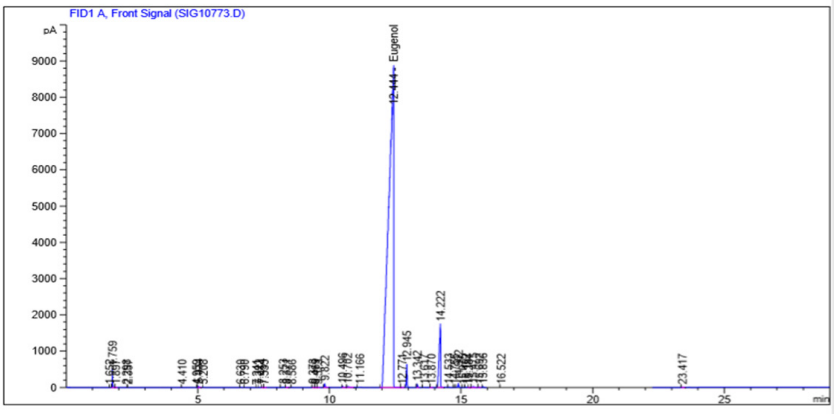

Figure 2. GC chromatogram of clove bud essential oil obtained by hydro-distillation.

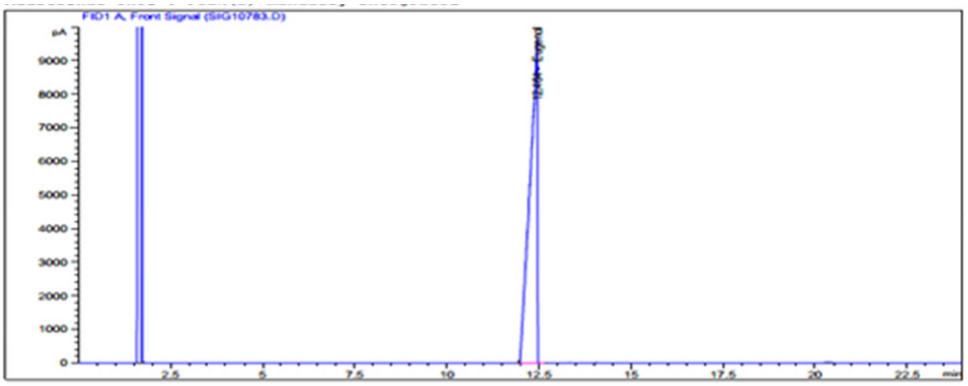

Figure 3. GC-FID chromatogram analysis of the eugenol as standard.

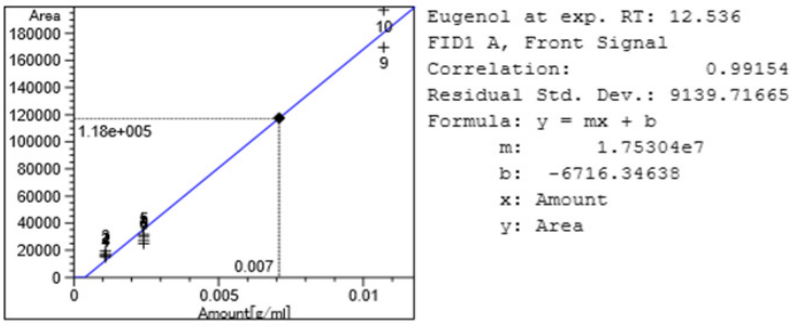

Figure 4. Calibration curve of eugenol and related equation.

Clinical trial results

From the total 38 enrolled patients, 22 completed the study (Figure 5). Analysis of the demographic data showed no significant difference between the groups (Table 2).

The mean of IELT before the intervention was not significantly different between the groups (p-value = 0.086). However, it was significantly (p-value = 0.003) improved in the clove gel comparing to the placebo group after 8 weeks of intervention (Table 3). In addition, 90.91% of the patients in the clove gel group experienced an increase of IELT at the end of study.

Table 4 compare the changes of PEDT scores in the study groups. While the difference of the groups was not significant at the beginning of the study, it became statistically significant after the intervention (p-value = 0.047). Improvement of PEDT score in clove gel group was significant comparing to the placebo group (p-value = 0.001).

Results of IIEF questionnaire are shown in Table 5. None of the IIEF items were changed significantly except for "Intercourse Satisfaction" which had a significant change in clove gel group comparing to the placebo group (p-value = 0.016).

It should also be mentioned that patients did not report any side effect during this study

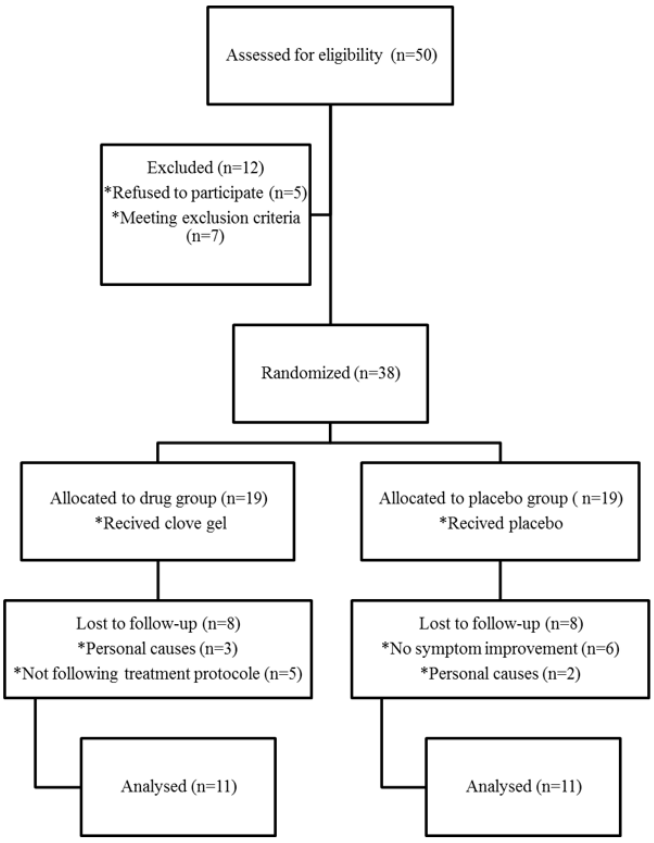

Figure 5. CONSORT diagram of the study

Table 2. Demographic characteristics of Clove gel and placebo groups

Variable	Intervention		*p*-value
	Placebo	Clove gel	
Age (year)	33±4.24	34±3.6	0.478†
BMI (Kg/m2)	24.8±1.2	24.32±1	0.797†
Age difference between man and his wife (year)	3±2.23	3.09±4.13	0.562†
Duration of marriage (year)	8.18±4.73	8±4.05	0.999†
Educational degree-associate of arts and lower	6(54.60)	3(27.30)	
Educational degree-high school diploma and higher	5(45.40)	8(72.70)	0.387‡

BMI: Body Mass Index; †Mann-Whitney Test; ‡Fisher's Exact Test

Table 3. Comparison of IELT in clove gel and placebo groups

	IELT (s) before the intervention (mean±SD)	IELT (s) after the intervention (mean±SD)	IELT (s) difference (mean±SD)
Clove gel group	29.85±18.59	97.1±91.86	67.24±900.1
Placebo group	42.51±13.98	52.45±32.7	9.93±25.54
P-value†	0.101	0.133	0.007

IELT: Intravaginal Ejaculation Latency Time; SD: Standard Deviation; †Mann-Whitney Test

Table 4. Comparison of PEDT scores in clove gel and placebo groups.

	PEDT score before the intervention (mean±SD)	PEDT score after the intervention (mean±SD)	PEDT score difference (mean±SD)
Clove gel group	14±3.55	9.2±4.56	-4.8±2.56
Placebo group	14.6±3.61	13.5±3.78	-1.1±0.94
P-value†	0.652	0.047	0.001

PEDT: Premature Ejaculation Diagnostic Tool; SD: Standard Deviation; †Mann-Whitney Test

Table 5. Comparison of IIEF scores in clove gel and placebo groups.

	Before the Intervention			After the Intervention			Difference		
IIEF Item	Clove gel group (mean±SD)	Placebo group (mean±SD)	*P*-value†	Clove gel group (mean±SD)	Placebo group (mean±SD)	P-value†	Clove gel group (mean±SD)	Placebo group (mean±SD)	P-value†
Erection Function	25.20±3.22	25.50±3.59	0.797	25.60±3.07	25.30±3.50	0.898	0.50±0.82	-0.20±0.60	0.193

Sexual Desire	7.10±1.04	7.50±1.51	0.606	7.30±0.90	7.50±1.57	0.797	0.20±0.40	0.00±0.45	0.519
Orgasmic Function	8.10±0.83	7.30±1.35	0.151	8.10±0.83	7.40±1.36	0.243	0.00±0.00	0.10±0.30	0.748
Intercourse Satisfaction	9.30±1.90	9.00±2.37	>0.999	10.40±1.50	9.00±2.32	0.332	1.10±1.41	0.00±0.45	0.016
Overall Satisfaction	6.20±1.83	5.60±1.91	0.606	7.50±1.29	6.10±1.87	0.065	1.40±1.57	0.50±0.82	0.243

IIEF: International Index of Erectile Function; SD: Standard Deviation; †Mann-Whitney Test

Discussion

For the first time, this study evaluated the effect of clove oil gel on premature ejaculation through a clinical trial. The comparison of the mean scores of the PEDT questionnaire before and after the intervention showed that the use of clove gel significantly improved the premature ejaculation. This index improved in the clove gel group from the disease range (above 11) to the range of probable PE. However, it remained unchanged in the placebo group. In addition, clove gel was able to significantly increase the IELT in comparison to the placebo. It could be a good explanation for the meaningful improvement of "Intercourse Satisfaction" in the intervention group.

Topical anesthetic formulations are considered as first-line treatment for PE with limited adverse events [28]. Nevertheless, topical natural products have also been evaluated for PE treatment in addition to the chemical drugs. A preliminary observational study on a topical formulation (in spray dosage form) included clove oil has shown beneficial effects in PE patients. In this study, patients with PE were asked to use two puff of this spray in the penile area and massage it 10 minutes before the intercourse for 30 days. Follow-up of the 28 enrolled patients revealed significant decrease of PEDT score and increase of IIEF [29]. In a recent clinical trial, two puffs of a topical polyherbal spray which included extracts of olive fruit oil (Olea europaea L.), black cumin seed oil (*Nigella Sativa* L.), and frankincense oleo-gum-resin (*Boswellia* sacra Flueck) was used every night and half an hour before each sexual intercourse for three weeks. Although the changes of IELT and PEDT total scores were not significant, its PE frequency and interpersonal difficulty items were improved [30]. Such different results of similar studies in comparison to the current trial could be due to the differences of the dosage forms, ingredients of the natural products, and the studied populations and their related cultural and physical factors.

Phenylpropanoids such as carvacrol, thymol, eugenol, and cinnamaldehyde are reported as the main components of clove essential oil [19]. Our analysis showed that the main components are eugenol, eugenol acetate, octan, e-caryo-

phyllene. Among them, eugenol was the major component (89.46%) as reported by similar studies [19,31].

EC possesses various pharmacological effects including local anesthetic and analgesic properties [32]. On the other hand, eugenol enhances the skin permeation in addition to its anti-oxidant and anti-inflammatory properties [31]. Therefore, it can affect the absorption of SA topical formulation.

The other component of clove oil, thymol, is a monoterpen with anti-oxidant, anti-inflammatory, analgesic, and anesthetic effects which also improves blood circulation [33,34]. Carvacrol, which is a phenol isomer of thymol, has also anti-oxidative, anti-spasmodic, and anesthetic effects [35].

Methyl salicylate is the other ingredient of SA essential oil which exerts anti-inflammatory and analgesic effects by inhibiting pro-inflammatory cytokines and suppressing the activation of the nuclear factor kappa B (NF-kB) signaling pathway [36].

Considering the components of the essential oil of the clove and their mentioned properties, it could be suggested that the clove oil gel may act with a sense decreasing effect as one of its mechanisms of action. The effect of clove oil in improving premature ejaculation can also be attributed to the stimulation of the nervous system and its effects on the neurotransmitter level [22].

Comparing to the other topical medications used for premature ejaculation, clove oil has not been reported to have any side effect such as numbness, vaginal discomfort, or dysuria. Accordingly, it could be considered as a natural complementary therapy in PE patients.

Limitations of the study

Main limitation of this study was the drop-out rate which was due to the non-compliance of the participants. Considering the cultural aspects, it could be the result of inconvenience caused by the intervention and its related assessments. Moreover, it was a pilot study with a small sample size and consequently could only suggest further trials for confirming the efficacy of treatment despite its affirmative results.

Conclusion

This investigation suggests that clove oil gel could improve premature ejaculation with no serious adverse effects. It could be a suitable candidate for future studies and can be considered as a complementary treatment for this disorder. However, further investigations with larger group of participants are needed to rigorously confirm its efficacy and safety.

Conflict of Interest

None.

Acknowledgments

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