Received: 28 January 2022 | Revised: 11 October 2022 | Accepted: 16 October 2022

DOI: 10.1002/ptr.7691

RESEARCH ARTICLE

WILEY

Efficacy of frankincense-based herbal product in urinary incontinence: A randomized, double-blind, placebo- and active-controlled clinical trial

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Funding information
Kerman University of Medical Sciences, Grant/Award Number: 97000624

Abstract

Urinary incontinence is a silent epidemic that has a serious impact on a person's quality of life (QOL). This study aimed to evaluate the efficacy of frankincense-based herbal product (FHP) in urinary incontinence compared with placebo and solifenacin. In this randomized, double-blind clinical trial, 120 postmenopausal women with mixed urinary incontinence were randomized to one of the three groups of FHP, placebo, and standard treatment (solifenacin). Frequency, amount of leakage, and score of urinary incontinence as well as the QOL were measured at the end of the second and fourth weeks and 2 weeks after the interruption of the treatment. The ICIQ-UI SF and I-QOL questionnaires were used for the measurements. Mean frequency of urinary incontinence and amount of leakage significantly decreased in the FHP and solifenacin groups in the fourth week compared to the placebo group. In addition, 2 weeks after treatment completion, the effects of the FHP were significant compared to the solifenacin group. Due to the effect of FHP on improving the QOL and also the prolonged effect of this drug, the use of FHP in urinary incontinence, as a complementary treatment could be suggested.

KEYWORDS
Boswellia sacra, frankincense, piperine, quality of life, urinary incontinence

1 | INTRODUCTION

One of the most common complaints of women in middle and old ages is urinary incontinence, which refers to any involuntary leakage of urine (Haylen et al., 2016). The prevalence of urinary incontinence in women is almost two times higher than men (Bauer & Huebner, 2013). The global prevalence of urinary incontinence in women of all ages has been reported to be 15%–50% (Brubaker et al., 2009; Daneshpajooh, Naghibzadeh-Tahami, Najafipour, & Mirzaei, 2021; Pal, Halder, & Bandyopadhyay, 2020). It is considered as a silent epidemic because

many women consider urinary incontinence as a normal process in their lives and some of them refuse to follow and treat the disease due to shame and modesty (Ahmadi et al., 2010). Urinary incontinence due to its nature leads to physical, mental, and psychological damages to the affected person, causes social isolation and reduces quality of life (QOL); in addition, it imposes many direct and indirect costs on the individual and society (Mallah et al., 2014; Wood & Anger, 2014). The three main types of urinary incontinence include: Stress urinary incontinence (SUI) involves urinary incontinence due to increased intra-abdominal pressure such as cough, laughter, exercise, and so forth, urge urinary incontinence (UUI) refers to urinary incontinence with or following a feeling of the urgent need to urinate, and mixed urinary incontinence (MUI) involves involuntary urination with increased intra-abdominal pressure and a feeling of the urgent need to urinate (Partin, Wein, Kavoussi, Peters, & Dmochowski, 2020). In Asia, the prevalence of MUI, UUI, and SUI is 63%, 23%, and 13.1%, respectively. According to statistics, the global prevalence of MUI varies from 14% to 61% (Kopańska et al., 2020), and on average about 21%–33% of the world's population suffers from MUI (Sun, Liu, Chen, Yan, & Liu, 2021). According to studies, MUI has more negative effects on a person's QOL than other types, and the severity of symptoms is higher in this type of urinary incontinence (Hansson Vikstrom, Wasteson, Lindam, & Samuelsson, 2020; Minassian, Devore, Hagan, & Grodstein, 2013). Treatment for MUI, depending on the predominant type, includes maintenance and supportive therapies, pharmacotherapy, and surgery (Porena, Costantini, & Lazzeri, 2013). Antimuscarinics, such as solifenacin, are the first line of pharmacotherapy in MUI with urge predominance, but have annoying side effects such as constipation, dry eyes and tongue, and so forth (Chughtai et al., 2013). On the other hand, surgical treatments also have short-term or long-term side effects, and the surgery success rate in this type is 26% lower than MUI with the dominance of SUI (Sun et al., 2021). Despite the advances in the treatment of urinary incontinence, due to the lack of complete knowledge of the pathophysiology of this problem as well as pharmacological and surgical complications, finding new treatment strategies, including complementary and alternative medicine, has always been considered. Given the World Health Organization's support for the use of complementary medicine and allowing the research of medicinal herbs based on specific protocols, the use of traditional medicine treatments as a complementary medicine seems reasonable (Arunachalam & Rothschild, 2015; Chughtai et al., 2013). In this regard, one of the treatments emphasized in traditional Persian medicine sources is frankincense-based herbal product (FHP) (Aghili Khorasani, 2015; Chashty, 2005). Therefore, in the present study, the efficacy of frankincense-based herbal product in women with MUI was evaluated in comparison with the standard drug solifenacin and placebo.

2 | MATERIALS AND METHODS

2.1 | Trial design

The current study was designed as a randomized, double-blind, placebo- and active-controlled clinical trial. It was in compliance with the Declaration of Helsinki (1989 revision) (World Medical Association, 2013) and was reviewed, approved, and monitored by the ethics committee of Kerman University of Medical Sciences (License number: IR.KMU.REC.1397.402). The trial was registered by the Iranian Registry of Clinical Trials with the following code: IRCT20190310042998N1. No changes were made in the methods after trial commencement.

2.2 | Participants

This study was performed on postmenopausal women with MUI who referred to Besat clinics in Kerman from January 2020 to June 2021. All cases were diagnosed by the urologist and gynecologist, according to history, physical, and pelvic examination, and if necessary, urodynamic test, urinary and pelvic ultrasound and laboratory tests such as U/A and U/C. Patients participated in the study after completing informed consent form if they met the inclusion criteria.

In this study, postmenopausal women aged 55–80 years with MUI with urge predominance were included in the study. Participants were excluded from the study if they met the following criteria: neurogenic bladder, pelvic organ prolapse (POP ≥ stage 2), urinary tract and vaginal infections, taking medicines in the past month to treat this disorder, receiving any type of conservative management therapies concurrently, including behavioral and physical therapy for urinary incontinence, neurological diseases, contraindications for anticholinergic use, drug addiction, history of pelvic radiotherapy, and chemotherapy, history of urogenital cancer, psychological disorders such as Alzheimer disease, severe gastrointestinal problems such as gastric ulcers, uncontrolled systemic diseases, refusal to participate in the study, drug intolerance, and the occurrence of drug allergy symptoms.

2.3 | Preparation of drugs and placebo

2.3.1 | Plant materials

The herbal materials were purchased from local markets in Kerman, Iran. They were identified at Herbal and Traditional Medicines Research Center (HTMRC), Kerman University of Medical Sciences, Kerman, Iran, and the specimens were deposited at HTMRC Herbarium for further reference (No. H 101–H 107 for Frankincense or Kondor (*oleo-gum-resin of Boswellia sacra Flueck from* Burseraceae) (K), sedge or Soed-E-Kofi (rhizomes of *Cyperus rotundus* L. from Cyperaceae) (S), Aucklandiae or Qust-E-Shirin (radix of *Dolomiaea costus* [Falc.] Kasana & A.K.Pandey from Asteraceae) (Q), the thin inner woody hulls of oak fruits or Jaft-E-Baloot (testa of *Quercus infectoria* Oliv. from Fagaceae) (J), long pepper or Darfelfel (fruit of *Piper longum* L. from Piperaceae) (D), black pepper or Felfel–Siah (fruit of *Piper nigrum* L. from Piperaceae) (F), and ginger or Zanjebil (rhizome of *Zingiber officinale* Roscoe from Zingiberaceae) (Z), respectively).

2.3.2 | Chemicals

Sucrose, corn starch, barley flakes (rolled barley), and dark brown food color 5,037/M were acquired from Shad-Shirin Sirjan Co., Mahshad Yazd Co., Aasan Co., and Abyaz-Chimie Co. (Iran), respectively. Magnesium stearate was from Sunhere Co. (China). Solifenacin succinate was supplied by BePharm, Ltd. (China). The Folin–Ciocalteu reagent and other chemicals and solvents were provided from Merck (Germany).

2.3.3 | Instrumentation

The hardness of the tablets was determined using a hardness tester (TB H28, Erweka, Germany). Friability, disintegration, and dissolution test apparatuses were procured from Noavaran Co. (Iran). The tablets were pressed using a single-punch tablet machine (Hasani Co., Iran). A spectrophotometer (model UV-1601 Shimadzu, Japan) was used for absorbance measurements.

2.3.4 | Preparation of frankincense-based tablets

According to traditional prescriptions, for each 650-mg tablet, the following formula was applied: K, S, Q, J, and D 100 mg/tablet, F and Z 40 mg/tablet, and sucrose and magnesium stearate 58 and 12 mg/tablet, respectively. Enough proportions of each of the seven plants were powdered (80-mesh sieve). Simple syrup (sucrose: water in a ratio of 2:1) was used in the formula to produce granules. The granules were dried and passed through sieve no. 14 and then magnesium stearate was added to the granules. The formulation was pressed by a concave, round, single-punch tablet machine. Then the physical properties of the tablets were evaluated. The amount of active constituents in each tablet was considered to be 580 mg. The usual dosage of this formulation prescribed in Iranian traditional clinics is 2–3 g/day (three tablets twice a day).

2.3.5 | Preparation of solifenacin and placebo tablets

For each 650-mg solifenacin tablet, the following formula was applied: Solifenacin succinate 1.2 mg/tablet, sucrose and magnesium stearate 58 and 12 mg/tablet, respectively, and an equal proportion of corn starch and barley flakes up to 650 mg. Placebo tablets were formulated without solifenacin. Other procedures were performed the same as frankincense-based tablet preparation.

2.3.6 | Quality control of frankincense-based and solifenacin succinate tablets

The prepared tablets (frankincense-based and solifenacin) underwent various physiochemical tests, microbiological limit tests, and assessment of pharmaceutical parameters, including appearance, diameter, thickness, weight variation, friability, disintegration time, hardness, and dissolution behavior, as well as the assay of total tannins, according to United States Pharmacopeia (USP) (United States Pharmacopeia and National Formulary (USP 39- NF *34*), 2016).

2.3.7 | Assay total tannins as gallic acid equivalents in frankincense-based tablets

Since tannins are the main constituent of the tablets, the content of total tannins in tablets as mg/g gallic acid equivalents (*GAE*) was assessed according to British Pharmacopoeia (BP) (British Pharmacopoeia Commission, 2015). Briefly, 80 ml of water was added to 100 mg of 10 powdered tablets and heated for 30 min. Then the mixture was diluted to a volume of 100 ml with water. Afterward, 2 ml of this solution was mixed with 1 ml of the Folin–Ciocalteu reagent and 10 ml of water and diluted to 25 ml with 29% solution of sodium carbonate. After 30 min in a dark place, the absorbance was measured at 760 nm using water and reagents as blank. The total tannins content of the frankincense-based tablet was determined by using the calibration curve of gallic acid as the standard material. The standard curve was prepared using 0, 12.5, 25, 50, and 100 mg/L solutions of gallic acid in the methanol/water mixture (50:50, v/v). The total phenolic content was expressed as mg/g equivalents of gallic acid using the following equation based on the calibration curve: $y = mx + c$ (y = absorbance, m = slope, x = concentration, c = intercept), which is a common reference compound.

2.3.8 | Assay of solifenacin

Thirty tablets were powdered, and 10 mg equivalent weight of the solifenacin tablet powder was accurately weighed and transferred into a 100-mL flask containing 40 ml of double-distilled water and sonicated for 10 min. The resultant solution was filtered into another 100-mL volumetric flask. The washings were added to the filtrate and the final volume was brought up to the mark with double-distilled water. Then 3 ml of the filtrate from the sample solution was diluted to a final volume of 10 ml with double-distilled water. Other procedures were continued according to the reference and the sample solution was analyzed spectrophotometrically at 412 nm (Singh & Nanda, 2011).

2.3.9 | Dissolution test of tablets

Dissolution test was performed on six tablets. The USP apparatus 2 (paddle) at a speed of 100 rpm with 900 ml of distilled water as the dissolution medium at 37°C was used and the samples were analyzed after 30, 45, and 60 min. The percentage of released total tannins was determined using 5 ml of the filtered portions of the samples.

2.3.10 | Stability assessment of frankincense-based tablets

Laboratory accelerated stability test was performed on frankincense-based tablets. Fifty tablets were packed in a polyethylene container and kept at a temperature of 40 ± 2°C and humidity of 75% ± 5% for 6 months. Then the characteristics of the tablets were determined (European Medicines Agency, 2003).

2.3.11 | High-performance thin-layer chromatography (HPTLC) analysis and Fourier transform infrared (FT-IR) spectroscopy

Extract preparation

Each sample (0.5 g of K, S, Q, J, D, F, Z, and two tablets) was separately dispersed in HPLC grade methanol (5 ml) and sonicated for 20 min (40°C). The solutions were then centrifuged at 3000 rpm for 20 min and the upper layer was used for HPTLC analysis and after drying (40°C), for FT-IR spectroscopy.

HPTLC fingerprint analysis

To develop a characteristic fingerprinting profile of the samples, chromatography was performed on pre-coated Aluminium HPTLC Silica gel 60 F_{254} plates (10 × 10 cm; E. Merck, Germany). The plates were pre-washed with methanol and dried in an oven at 105°C. Thereafter, 10 µl of each sample and piperine (P), resveratrol (R), gallic acid (Ga), linalool (L), and tannic acid (Ta) as standards (2 mg/mL) were applied as bands of 5 mm using a 25-µL syringe. Linear ascending development was carried out in a developing chamber (CAMAG, Switzerland) saturated with the mobile phase for 20 min at room temperature (25°C) using a filter paper.

A mobile phase of ethyl acetate:toluene:methanol:formic acid (15:5:0.5:0.2, v/v/v/v) provided acceptable sample resolution. The plates were developed to a distance of 9.5 cm from the lower edge of the plate. Drying was carried out for 5 min at room temperature (25°C). Chromatograms were recorded at the wavelength of 254 nm. Then for derivatization, the plates were sprayed with natural products (NP) reagent (1% diphenylboric acid aminoethyl ester in methanol) and visualized under UV light (254 and 365 nm). For another derivatization, the plates were sprayed with vanillin-sulfuric acid reagent (1% vanillin in ethanol then 5% sulfuric acid in ethanol) (Va/Sa) followed by heating at 100°C for 5 min. Images of the chromatograms were electronically recorded using a digital camera. The retention factor (*Rf*) value of each main compound separated on the plates was recorded.

FT-IR fingerprint

FT-IR data were acquired using an FT-IR spectrometer. For sampling techniques, the KBr method was employed. Each sample was grounded using an agate mortar and pestle to obtain a very fine powder. Afterward, 2 mg of the fine powder samples was mixed with about 100 mg of dried potassium bromide salt. Each mixture was then pressed under a hydraulic press using a die to yield a transparent disc (measuring about 13 mm in diameter and 0.3 mm in thickness) through which the beam of spectrometer passed. The analysis was performed using a BRUKER Alpha (Germany) FT-IR spectrometer.

2.4 | Intervention

Eligible participants were divided into three parallel groups. In this study, patients received 6 tablets of 650-mg FHP, solifenacin or placebo (3 after breakfast and 3 after dinner). No concomitant medication was allowed.

2.5 | Outcome measures

Primary outcomes included changes in the frequency of urinary incontinence and amount of leakage, which were assessed using the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) (Hajebrahimi, Nourizadeh, Hamedani, & Pezeshki, 2012). Secondary outcomes included changes in urinary incontinence scores and QOL, which were assessed by a trained physician using ICIQ-IU SF and Incontinence Quality of Life (I-QOL) questionnaires, respectively (Kurzawa, Sutherland, Crump, & Liu, 2018; Nojomi, Baharvand, Moradi Lakeh, & Patrick, 2009). This information was collected before the intervention, at the end of weeks 2 and 4, and also, 2 weeks after discontinuation of treatment (week 6) for follow-up.

2.6 | Sample size

Based on the formula for calculating the sample size for comparing the two ratios, and considering the study power of 90% and the minimum effect size of 25%, 28 people were considered in each group, and considering 10% loss to follow up, and the fact that this trial included three groups, the sample size was corrected and 40 people were considered for each group.

2.7 | Safety assessment

At the beginning of the study and in the fourth week, serum levels of blood urea nitrogen (BUN), creatinine, serum glutamate pyruvate transferase (SGPT), serum glutamate oxaloacetate transferase (SGOT), alkaline phosphatase (ALP), total and direct bilirubin and complete blood count (CBC) were measured in patients. The participants were asked to report any side effects while taking the medication.

2.8 | Randomization and blinding

One hundred and twenty patients were randomly divided into three groups: FHP, solifenacin, and placebo groups (40 patients in each

group). Block randomization using computer-generated random numbers with a block size of six was used for treatment assignment.

The tablets were packed in a container by a pharmacist. Each drug container was labeled by a code number, and the contents of the containers were distributed according to the randomization list, independent of the investigator and the participating clinicians.

The study was double-blinded; hence, the patients, investigators, study team, and data analyzer were not aware of the treatment group allocation.

2.9 | Statistical method

Age, BMI, marital status, number and type of delivery, history of pelvic trauma, history of surgeries such as hysterectomy, occupation, level of education and duration of urinary incontinence among patients were evaluated in the three groups using analysis of variance and Chi-square test. To statistically compare the frequency, amount of leakage, score of urinary incontinence, and QOL in the three groups at four different times (at time of registration, weeks two, four, and six), Kruskal–Wallis, Friedman and Wilcoxon-Mann–Whitney tests were used. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) software version 21. Statistical significance was considered at $p < .05$.

3 | RESULTS

3.1 | Pharmaceutical characterization

As tannins are the major chemical components of the frankincense-based tablet, it was logical to evaluate the prepared tablets in terms of the tannin content. Therefore, these chemical constituents were considered to be the marker for assays and dissolution studies of tablets. The results showed that the tablets contained a remarkable amount of tannins and these chemicals were released from the tablets during 60 min (acceptance level: minimum 75%). The content of phenolic compounds (mg/g GAE) was determined from regression equation of the calibration curve ($y = 0.0077x + 0.0069$, $R2 = 0.9999$) and expressed in terms of gallic acid equivalents (GAE). The total phenolic content of each frankincense-based tablet was 90.42 ± 2.91 mg GAE.

All physicochemical properties of the prepared tablets were in agreement with the USP requirements for tablets (United States Pharmacopeia and National Formulary (USP 39- NF *34*), 2016). The results of physicochemical characteristics and accelerated stability test of frankincense-based and solifenacin tablets have been shown in Table 1. The results of the microbiological limit tests were in accordance with WHO guidelines (World Health Organization, 2011).

3.2 | HPTLC fingerprint analysis

Piperine is a pharmacologically active compound isolated from frankincense-based tablets; D and F are detected by prominent spots. The *Rf* value was 0.65 for piperine in these samples. The visualization comparison spots and the obtained *Rf* values of all the extracts with frankincense-based tablets at UV254, UV254, and 366, NP/366, Va/Sa, and Va/Sa/UV366 nm are shown in Figure 1 and Table 2.

3.3 | FT-IR fingerprint

FT-IR spectroscopic studies have shown the existence of various chemicals in frankincense-based tablets. The IR spectra of P: piperine, R: resveratrol, Ga: gallic acid, L: linalool, Ta: tannic acid, K: *Boswellia sacra*, S: *Cyperus rotundus*, Q: *Dolomiaea costus*, J: *Quercus infectoria*, D: *Piper longum*, F: *Piper nigrum*, Z: *Zingiber officinale*, and T: frankincense-based tablets were recorded (Figure 2). The results of the FT-IR analysis of each peak value in response to the individual components are shown in Table 3.

TABLE 1 Physicochemical characteristics and accelerated stability test of frankincense-based and solifenacin tablets

Test[a]	Frankincense-based start/3 months/6 months	Solifenacin start/3 months/6 months
Appearance	Round, biconvex, brown tablet/same/same	Round, biconvex, brown tablet/same/same
Weight variation (mg)	650 ± 5% /same/ same	650 ± 5%/same/same
Thickness (mm)	4.55 ± 5%/same/same	4.04 mm ± 5%/same/same
Diameter (mm)	9.95 ± 2%/same/same	9.95 mm ± 2%/same/same
Disintegration time (min)	25.02 ± .21/25.04 ± 0.11/24.09 ± 0.45	31.08 ± 0.22/30.22 ± 0.45/30.05 ± 0.25
Dissolution, 60 min (%)	94.50 ± 0.45/96.14 ± 0.55/ 95.82 ± 0.65	97.22 ± 0.55/96.9 ± 0.65/ 95.23 ± 0.44
Hardness (kp)	16.09 ± 0.06 /15.45 ± 0.23/14.56 ± 0.24	19.22 ± 0.45/ 19.13 ± 0.45/ 18.09 ± 0.45
Assay of total tannins as gallic acid equivalents (mg/tablet)	90.42 ± 2.91/91.09 ± 1.51/89.69 ± 2.03	–
Assay of solifenacin (mg/tablet)	–	1.11 ± 0.05/1.02 ± 0.07/0.995 ± 0.06

[a]Data are expressed as Mean ± SD ($n = 6$). The stability results showed no significant differences after 6 months.

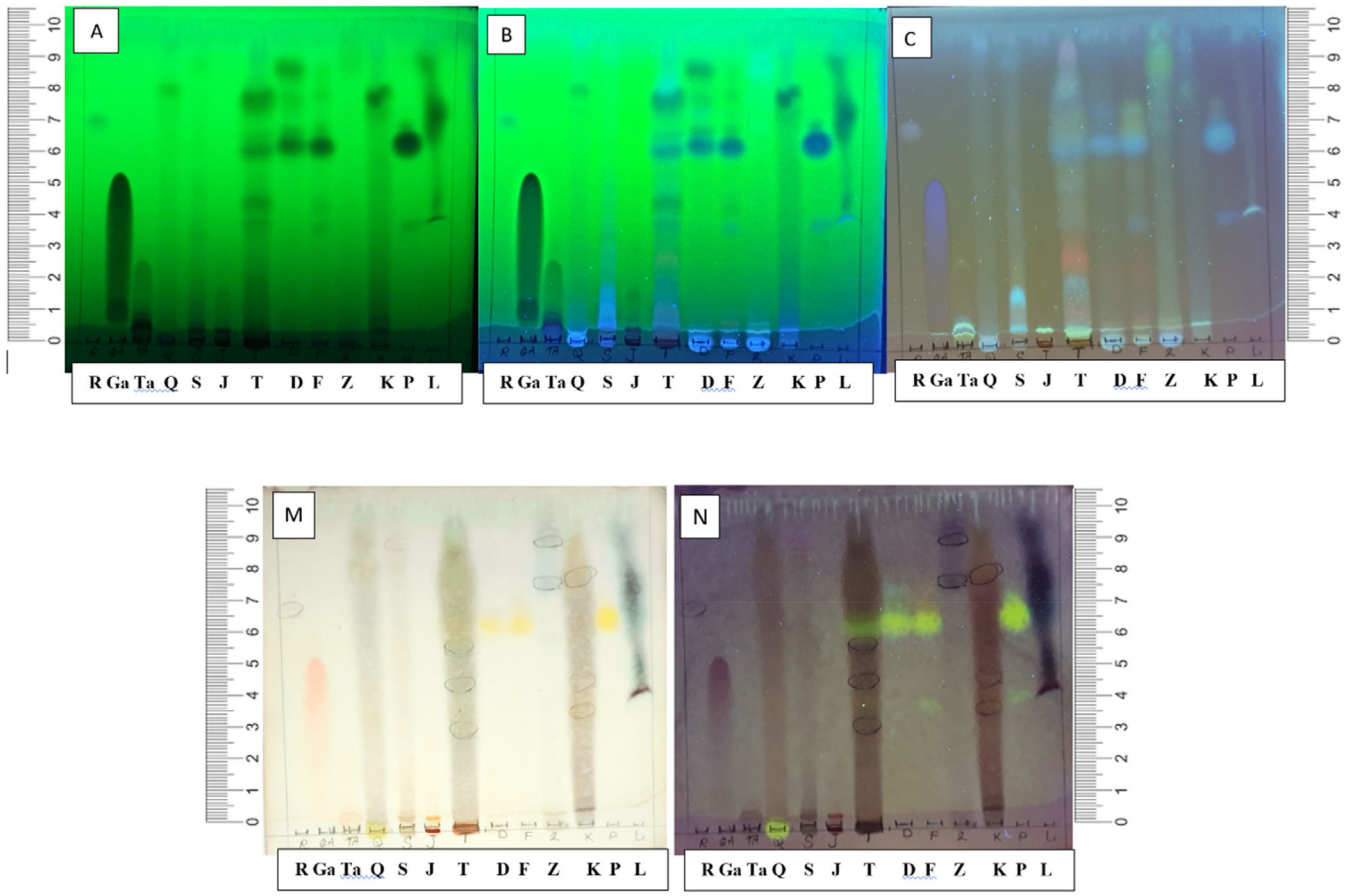

FIGURE 1 TLC visualization comparison spots of all the extracts with frankincense-based tablets. P: piperine, R: resveratrol, Ga: gallic acid, L: linalool, Ta: tannic acid, K: *Boswellia sacra*, S: *Cyperus rotundus*, Q: *Dolomiaea costus*, J: *Quercus infectoria*, D: *Piper longum*, F: *Piper nigrum*, Z: *Zingiber officinale*, and T: frankincense-based tablets; Mobile phase: ethyl acetate: toluene: methanol: formic acid (15:5:0.5:0.2, v/v/v/v); Stationary phase: Aluminium HPTLC Silica gel 60 F_{254} plates; Detection: A: UV254, B: UV254&366, C: Natural products reagent/ UV366, M: vanillin-sulfuric acid reagent and N: vanillin-sulfuric acid reagent/UV366

3.4 | Participants' enrollment

In this study, 609 women with MUI were initially screened for eligibility. Finally, 120 patients with urinary incontinence were enrolled in the study. In the FHP group, 7 people (5 people due to drug side effects including heartburn, diarrhea, skin rash, itching and nausea and 2 people due to unwillingness to continue the intervention), in the solifenacin group, 6 people (5 patients due to drug side effects including severe dry mouth and abdominal pain and 1 patient due to unwillingness to continue the intervention) and 6 people in the placebo group (due to unwillingness to continue the intervention) were excluded from the study. Detailed description of the patients' enrolment, randomization and analysis is illustrated in Figure 3.

3.5 | Basic characteristics

Clinical and demographic characteristics of patients at the beginning of the study in all three groups are presented in Table 4. There was no significant difference in age, BMI, education level, occupational status, marital status, number of normal vaginal deliveries and cesarean section, history of pelvic trauma, history of hysterectomy and duration of urinary incontinence between the three groups. In addition, the outcomes studied in the baseline were similar in all three groups.

3.6 | Clinical response

As presented in Figure 4 and Table 5, within group comparison in the FHP group showed that reduction of mean frequency of urinary incontinence and amount of leakage, decrease of urinary incontinence score according to the ICIQ-SF questionnaire and improvement of QOL according to the I-QOL questionnaire in the second and fourth weeks of intervention as well as 2 weeks after discontinuation of the treatment (sixth week) were notably significant. In the solifenacin group, a significant decrease in the mean frequency and amount of urine leakage, as well as the ICIQ-UI SF questionnaire score was observed in the second, fourth, and sixth weeks, but the I-QOL questionnaire score in the second and fourth weeks showed a significant

TABLE 2 *Rf* values of various bands in the TLC fingerprint of all the extracts with frankincense-based tablets

Detection method	Rf/color	T	S	Q	J	K	Z	F	D	Ta	P
Va/Sa	0.05/red	*			*					*	
NP/UV366	0.05/yellow	*			*					*	
UV254	0.00–0.15/quenching	*			*					*	
UV254&366	0.00–0.15/bright blue	*			*					*	
NP/UV366	0.15/azure	*	*								
NP/UV366	0.25/red	*						*			
Va/Sa	0.35/brown	*				*					
Va/Sa	0.45/brown	*				*					
UV254	0.65/quenching	*						*	*		*
UV254&366	0.65/dark blue	*						*	*		*
NP/UV366	0.65/blue	*						*	*		*
Va/Sa	0.65/dark yellow	*						*	*		*
Va/Sa/ UV366	0.65/bright yellow	*						*	*		*
UV254	0.75/quenching	*		*							
NP/UV366	0.75/yellow	*		*							
UV254	0.78/quenching	*				*					
NP/UV366	0.78/blue	*				*					
NP/UV366	0.90/yellow-orange	*					*				
UV254&366	0.90/bright blue	*					*				
UV254	0.90/quenching	*	*								
NP/ UV366	0.90/blue	*	*								
NP/UV366	0.95/bright blue	*		*							

Note: K, *Boswellia sacra*; S, *Cyperus rotundus*; Q, *Dolomiaea costus*; J, *Quercus infectoria*; D, *Piper longum*; F, *Piper nigrum*; Z, *Zingiber officinale*; T, frankincense-based; P, piperine; Va/Sa, vanillin-sulphuric acid reagent and NP, Natural products reagent.

decrease. In the placebo group, there was no significant change in these variables over time.

In the between group comparison, in both FHP and solifenacin groups, a significant reduction in the mean frequency of urinary incontinence and amount of leakage was observed in the fourth week compared to the placebo group, but 2 weeks after discontinuation of the intervention, this reduction was significant only in the FHP group. In the second and fourth weeks of the study, there was no difference between the FHP and solifenacin groups, while 2 weeks after stopping treatment, the frequency and amount of urine leakage were significantly lower in the FHP group.

The mean score of ICIQ-UI SF questionnaire in the FHP group in the fourth week and 2 weeks after discontinuation of treatment significantly decreased compared to the placebo group. In addition, 2 weeks after discontinuation of treatment, this mean showed a significant decrease in the FHP group compared to the solifenacin group. However, the mean score of the questionnaire in the solifenacin group was not significantly different compared to the placebo group.

The QOL in the FHP group in the fourth week compared to the placebo group and in the fourth week and 2 weeks after discontinuation of treatment compared to the solifenacin group decreased significantly. But the mean score of the questionnaire in the solifenacin group was not significantly different from the placebo group.

There was no significant change in the values of blood parameters measured in the FHP group compared to other groups. In the solifenacin group, the main drug side effects were gastrointestinal. Among these patients, 18 patients (45%) reported dry mouth, 8 (20%) constipation, 5 (12.5%) epigastric pain, 1 (2.5%) periumbilical pain, 1 (2.5%) dry eye, and 1 patient (2.5%) reported nausea. In the FHP group, 2 patients (5%) complained of heartburn, 2 (5%) reported burning mouth, 1 (2.5%) diarrhea, 2 (5%) periumbilical pain, 1 (2.5%) rash and itching, 1 (2.5%) cramp, and 1 patient (2.5%) also complained of tingling.

4 | DISCUSSION

In this double-blind clinical trial study, the efficacy of FHP in reducing the clinical symptoms of MUI in postmenopausal women and improving their QOL was investigated. The results of the present study showed that FHP compared to the placebo was effective in reducing the frequency, amount of urine leakage and score of urinary incontinence, as well as improving the QOL in patients. The decrease in these variables was also evident in the solifenacin group, indicating that FHP, similar to solifenacin, may be effective in reducing the symptoms of urinary incontinence. The results of evaluation of the I-

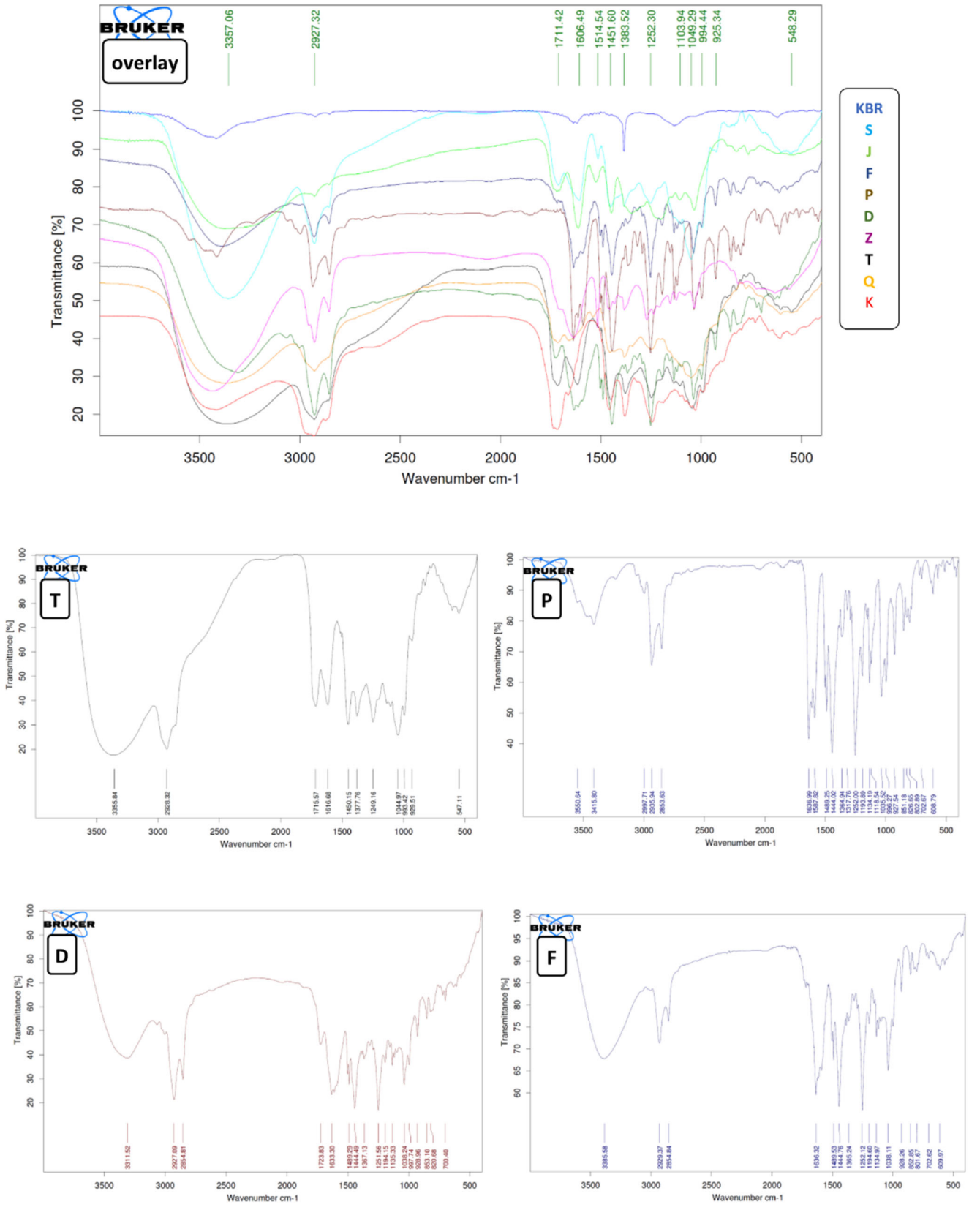

FIGURE 2 FT-IR spectra of frankincense-based tablets and the components. T: frankincense-based tablets, P: piperine, Ta: tannic acid, K: *Boswellia sacra*, S: *Cyperus rotundus*, Q: *Dolomiaea costus*, J: *Quercus infectoria*, D: *Piper longum*, F: *Piper nigrum*, and Z: *Zingiber officinale*

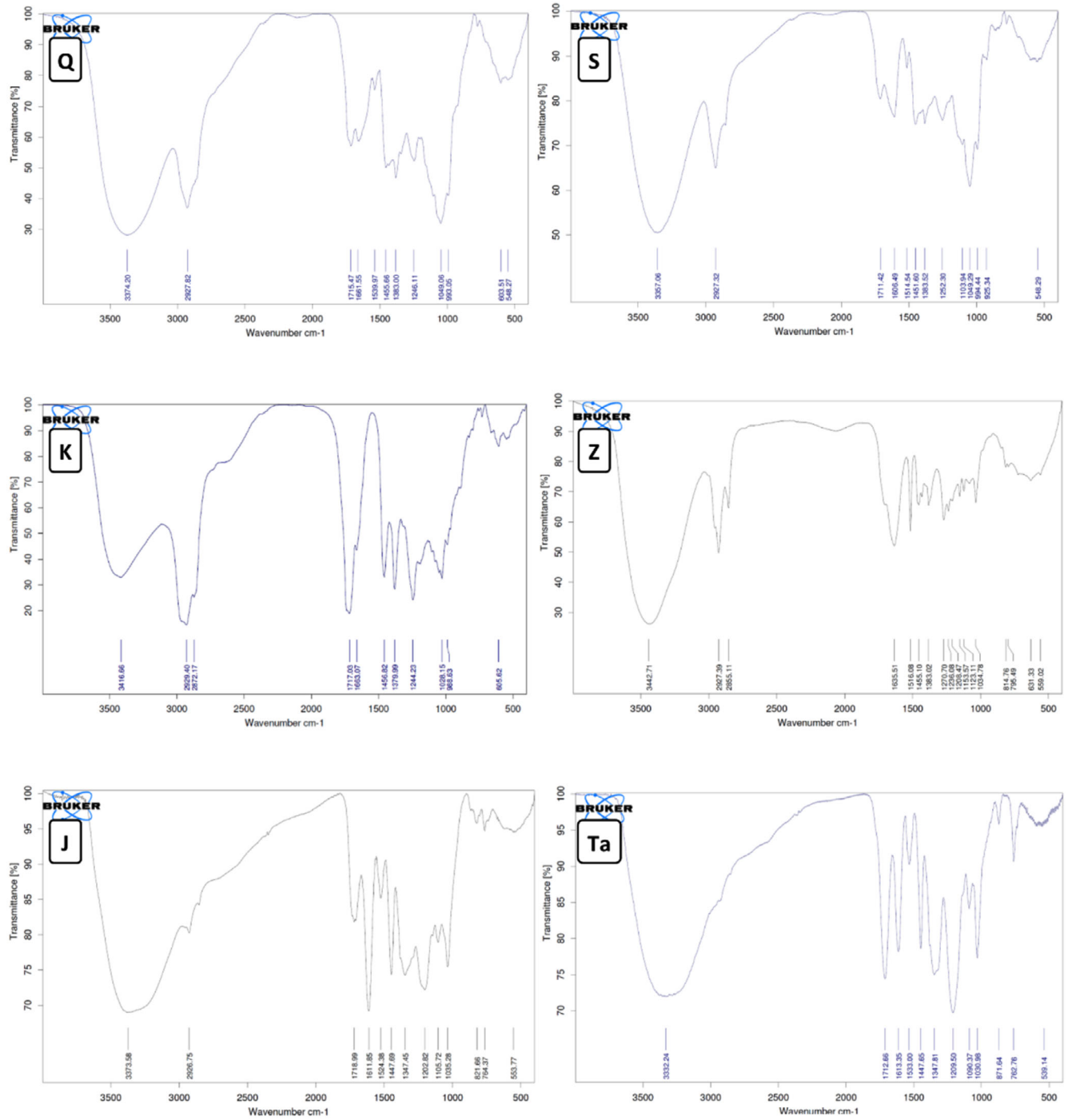

FIGURE 2 (Continued)

QOL questionnaire showed that the effect of FHP in the fourth week of the intervention, and also, 2 weeks after discontinuation of treatment was significant compared with the solifenacin group. This indicates that FHP is more effective in improving the QOL in a person with urinary incontinence and also leads to results lasting for at least 2 weeks after stopping treatment compared to the standard drug - solifenacin. Decreased QOL in patients with urinary incontinence due to neurological disorders such as depression, anxiety, decreased self-esteem, sexual problems, and decreased social relationships is of great importance. Among all types of urinary incontinence, MUI has the most negative impact on the QOL (Mallah et al., 2014; Welk & Baverstock, 2017).

In the present study, the mean BMI of the study participants was reported to be above 30. Several studies have reported a relationship between urinary incontinence and obesity (Aoki et al., 2017; Batmani, Jalali, Mohammadi, & Bokaee, 2021; Ebbesen, Hunskaar, Rortveit, &

TABLE 3 FT-IR peak ranges and their respective assigned functional groups

Sample; position (cm^{-1})	Range (cm^{-1})	Bond	Functional group
T; 929,993 P; 802,826,851,927,996 D; 820,853,928,997 F; 801,852,928 Q; 993 S; 925,994 K; 968 Z; 814 J; 821 Ta; 871	800–1,000	Out of plane C-H bending	Substituted phenyl
T; 1,044 P;1,035,1,116,1,134,1,193 D; 1,038,1,135,1,194 F; 1,038,1,134,1,194 Q; 1,049 S; 1,049,1,103 K; 1,026 Z; 1,034,1,123,1,153 J; 1,005,1,105 Ta; 1,030,1,090	1,000–1,200	C–N stretch C–O–C stretch In-plane CH pending modes	Primary amines Terpenoids, flavones
T; 1,249,1,377,1,450 P;1,262,1,317,1,364,1,444,1,489,1,587 D; 1,251,1,367,1,489 F; 1,252,1,365,1,444,1,489 Q; 1,246,1,383,1,455,1,539 S; 1,252,1,383,1,415,1,514 K; 1,244,1,379,1,456 Z; 1,208,1,236,1,270,1,383,1,455,1,516 J; 1,005,1,105 Ta; 1,202,1,347,1,447,1,524	1,200–1,600	C–H wag CH_2 deformation stretching Deformation asymmetric in plane C–N stretch Stretching of OCO CO stretching; CO linkages	Alkane or alkyl groups Lignin Xylan In methyl and phenol Aromatic amines I, II
T; 1,616,1715 P;1,636 D; 1,633,1723 F; 1,636 Q; 1,661,1715 S; 1,606,1711 K; 1,663,1717 Z; 1,635 J; 1,611,1718 Ta; 1,613,1712	1,600–1800	Carbonyl compounds C = O bond Absorbed OH and conjugated CO, HOH, OH bending R1R2C = CH2 C = O stretching C = O vibration Ortho-CO-C6H4-OH	Amides and esters In lignin or cellulose Absorbed water Methylene, overtone of δ'CH (out of plane) Ketone Influenced by I, M, and steric effects of substituent
T; 2,928 P; 2,853,2,935,2,997 D; 2,854,2,927 F; 2,854,2,929 Q; 2,927 S; 2,927 K; 2,872,2,929 Z; 2,855,2,927 J; 2,926 Ta; broad band	2,800–3,000	CH stretching	Alkane or alkyl groups
T; 3,355 (broad band) P;3,415,3,550 D; 3,311(broad band) F; 3,385(broad band) Q; 3,374(broad band) S; 3,357(broad band) K; 3,416(broad band) Z; 3,442(broad band) J; 3,373(broad band) Ta; 3,302(broad band)	3,200–3,400	O–H stretch, free hydroxyl	Alcohols, phenols

Note: T, frankincense-based tablets; P, piperine; Ta, tannic acid; K, *Boswellia sacra*; S, *Cyperus rotundus*; Q, *Dolomiaea costus*; J, *Quercus infectoria*; D, *Piper longum*; F, *Piper nigrum* and Z, *Zingiber officinale*.

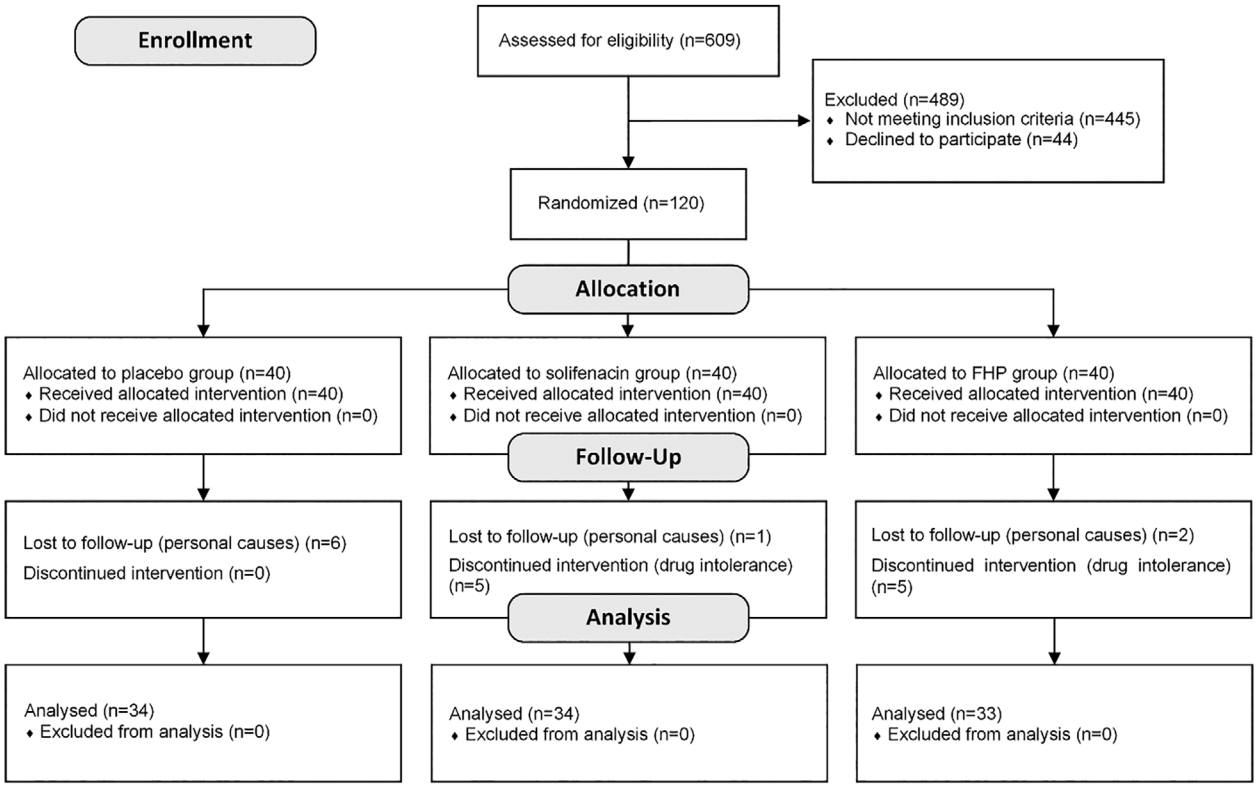

FIGURE 3 CONSORT flow diagram of the study

Hannestad, 2013). In a study by Ataweel et al. on women in Saudi Arabia, obesity was identified as one of the risk factors for urinary incontinence (Altaweel & Alharbi, 2012). Other causes of urinary incontinence in women include a history of normal vaginal delivery and/or history of hysterectomy. In the present study, the average number of normal vaginal delivery was over 3 and the percentage of hysterectomy was 19.7%. Other studies have shown the association between high parity and/or history of hysterectomy with the incidence of urinary incontinence in women (Aoki et al., 2017; Batmani et al., 2021; Ebbesen et al., 2013; Zhu et al., 2009).

This study is the first study that investigated the effect of a traditional product containing *Boswellia sacra* Flueck., *Cyperus rotundus* L., *Dolomiaea costus*, *Quercus infectoria* Oliv., *Piper longum* L., *Piper nigrum* L. and *Zingiber officinale* on MUI in postmenopausal women. Limited studies have been performed on the effects of herbal products on urinary incontinence. A single-blind clinical trial in Bangalore, India, evaluated the efficacy of an edible composition of *Boswellia serrata* and *Cyperus scariosus* plus pelvic floor muscle physiotherapy (PFMT) in the treatment of stress urinary incontinence in proactive women compared with placebo using a one-hour pad, indicating that this drug had higher efficiency compared to placebo ($p < .001$) (Arkalgud Rangaswamy, Sultana, Rahman, & Nagapattinam, 2014). In a study by Borrelli et al. the effect of *Boswellia serrata* gum resin extract (BSE) on in vivo and in vitro media on reduction of intestinal motility in diarrhea was investigated. BSE reduced acetylcholine-induced contractions in isolated guinea-pig ileum. The study of the effect of BSE on rodents showed an inhibitory effect on diarrhea. In their study, the effect of reducing intestinal contractions was attributed to 3-acetyl-11-keto-β-boswellic acid, which acts on L-type Ca^{2+} channels (Borrelli et al., 2006). One of the pathophysiological causes of urge urinary incontinence is bladder hypersensitivity. Urothelium acts as a strong thermal, mechanical, and chemical sensor, and the role of inflammation and infections in hyperactive bladder has been identified (Aoki et al., 2017). Piperine, the major alkaloid of *P. nigrum* and *P. longum* and the active compound isolated from frankincense-based tablets, exerts antiinflammatory effects through inhibiting activity of NF-κB, reducing expressions of TNF-&, IL-1ß, IL-6 (Wang et al., 2017). Furthermore, *Boswellia sacra* has a strong antiinflammatory effect (Alluri, Kundimi, Sengupta, Golakoti, & Kilari, 2020; Majeed, Majeed, Narayanan, & Nagabhushanam, 2019; Yu et al., 2020). Therefore, one of the reasons for the effectiveness of FHP in the treatment of urinary incontinence can be related to its antiinflammatory effect. In a double-blind clinical trial conducted by Niktabe et al. the effectiveness of topical application of *Dolomiaea costus*, formerly known as *Saussurea costus* or *Saussurea lappa*, compared with placebo was evaluated in women aged 30–70 years with MUI and SUI (Niktabe et al., 2018). In this study, in which the participants underwent intervention and were followed up 4 weeks after the intervention, the symptoms and frequency of urinary incontinence were reduced in the topical *Dolomiaea costus* oil recipients compared with the placebo recipients ($p < .001$). Although the action mechanism of FHP is not well understood, but one of the possibilities is that it works by inhibiting serotonin and noradrenaline reuptake. Studies have shown that piperine, a major component of FHP, has an anxiolytic and antidepressant effect

TABLE 4 Demographic data and baseline clinical characteristics of the patients participating in the trial

Variable	Group			*p*-value
	FHP ($n = 33$)	Solifenacin ($n = 34$)	Placebo ($n = 34$)	
Age[a]	62.48 ± 6.36	61.18 ± 6.14	61.79 ± 5.67	0.67
BMI (kg/m^2)	30.34 ± 5.00	32.26 ± 4.39	30.84 ± 4.81	0.09
Number of deliveries[a]				
Vaginal	3.58 ± 1.90	3.91 ± 3.33	3.18 ± 2.45	0.51
Cesarean	0.97 ± 0.52	1.01 ± 0.59	0.92 ± 0.62	0.90
Duration time of UI (year)[a]	6.25 ± 6.02	8.35 ± 6.92	10.45 ± 7.93	0.71
Marital status[b]				0.54
Married	32 (97%)	33 (97.1%)	34 (100%)	
Single	1 (3%)	1 (2.9%)	0 (0%)	
Occupation[b]				0.17
No	32 (97%)	34 (100%)	31(91.2%)	
Yes	1 (3%)	0 (0%)	3 (8.8%)	
Pelvic surgery[b]				0.58
Hysterectomy	5 (15.2%)	9 (26.5%)	6 (17.6%)	
Other				
Yes	11(33.3%)	8 (23.5%)	7 (20.6%)	
No	17 (51.5%)	17 (50%)	21(61.8%)	
Level of education[b]				0.47
Illiterate	6 (18.2%)	4 (11.8%)	3 (8.8%)	
Elementary school	8 (24.2%)	6 (17.6%)	8 (23.5%)	
Middle school	5 (15.2%)	13 (38.2%)	6 (17.6%)	
High school	9 (27.3%)	7 (20.6%)	10 (29.4%)	
Academic	5 (15.2%)	4 (11.8%)	7 (20.6%)	
History of pelvic trauma[b]				0.66
Yes	5 (15.2%)	3 (8.8%)	3 (8.8%)	
No	28 (84.8%)	31(91.2%)	31(91.2%)	

[a]Data are expressed as Mean ± SD.
[b]Data are expressed as number (%).

that is mediated through the regulation of the serotonergic system by enhancing 5-hydroxytryptamine content (Li et al., 2007; Mao, Xian, Ip, & Che, 2011). *Boswellia sacra* and *Cyperus rotundus* in combination with FHP have antidepressant, anti-anxiety, and sedative effects. Studies have shown the antidepressant and anti-anxiety effects of *Boswellia* species, and the neuroprotective effects of *B. serrata* on dopaminergic neurons (Moussaieff et al., 2008). Neuroprotective effects of different species of *Boswellia* in treatment of neurodegenerative diseases have been proven based on in vitro, laboratory, and clinical trials (Rajabian, Sadeghnia, Fanoudi, & Hosseini, 2020). Several studies have shown that *C. rotundus* has antidepressant effects by increasing serotonin and dopamine levels in the nervous system (Guan & Liu, 2016; Zhou et al., 2016). One of the compounds in FHP is *Quercus infectoria*. Various studies have shown the neuroprotective effect of *Quercus* species. Due to their compounds such as tannin, different species of *Quercus* have a therapeutic effect on urinary incontinence and are used as an astringent in treatment of uterine problems (Taib, Rezzak, Bouyazza, & Lyoussi, 2020). Many herbal medicines used in complementary medicine are used as a combination of different herbs, which can be due to the synergistic effect of different herbal compounds. Studies demonstrated that piperine is the most potent bioenhancer and it can increase bioavailability of different drugs (Atal & Bedi, 2010; Shao et al., 2015). According to a study by Vijayarani et al., the use of *Piper longum* with Boswellic acid in herbal products increases the bioavailability of the drug, which is related to the inhibition of cytochrome P450 enzyme (Vijayarani et al., 2020). *Boswellia sacra* in Ayurvedic medicine is considered as an astringent drug due to its compounds such as tannins and flavonoids (Siddiqui, 2011). Apart from *Boswellia sacra*, tannins and flavonoids are also found in various combinations of FHP such as *C. rotundus*, *Q. infectoria*, *D. costus*, *P. nigrum*, and *Z. officinale* (Abdallah, Qureshi, Ali, & Elhassan, 2017; Ahmad et al., 2015; Ghasemzadeh, Jaafar, & Rahmat, 2010; Kamala, Middha, Gopinath, Sindhura, & Karigar, 2018; Yusof & Abdullah, 2020). In studies on the medical treatment of MUI with the predominance of urge, and in UUI, the standard treatment is the use of antimuscarinics, including solifenacin; however, despite

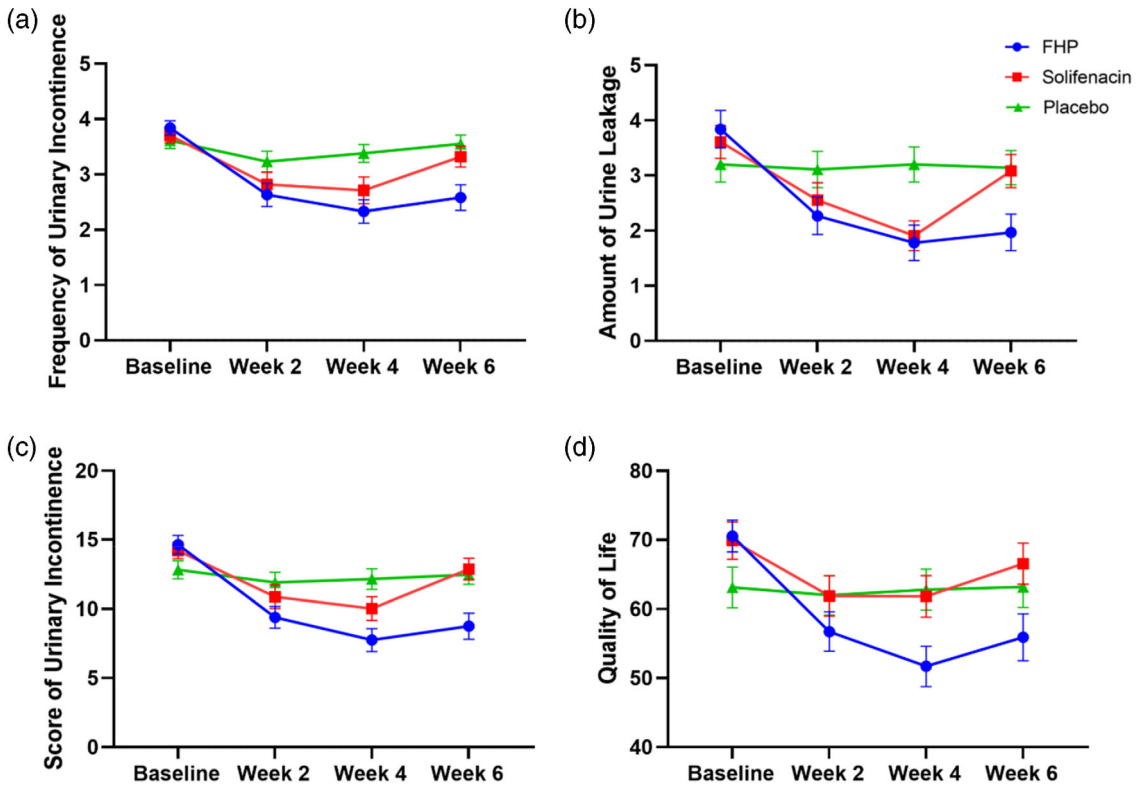

FIGURE 4 Change in all the variables in the FHP group from baseline (week 0) to weeks 2, 4, and 6 compared to the solifenacin and placebo groups. (a) Frequency of urine incontinence. (b) Amount of urine leakage. (c) ICIQ-UI SF questionnaire score. (d) Incontinence quality of life questionnaire score

high efficacy of solifenacin, side effects such as palpitations, tachycardia, constipation, dry mouth and eyes, as well as abdominal pain make it difficult for patients to tolerate this drug and lead to discontinuation of the drug (Y. F. Yu, Nichol, Yu, & Ahn, 2005). In the present study, gastrointestinal complications were reported by a significant number of patients, the most important of which were dry mouth (45%), constipation (20%), and epigastric pain (12.5%). In a meta-analysis by Vouri et al. on the side effects of antimuscarinics and discontinuation of the drug in old people compared to placebo, it was revealed that the most prevalent side effects were dry mouth and constipation (Vouri, Kebodeaux, Stranges, & Teshome, 2017). Several studies have shown the effect of *Boswellia sacra* in treatment of dementia and Alzheimer disease by reducing the activity of acetylcholinesterase (Murray, Faraoni, Castro, Alza, & Cavallaro, 2013). Since one of the problems of patients with Alzheimer disease is urinary incontinence and antimuscarinic drugs interact with drugs used to treat dementia, the use of FHP to treat urinary incontinence in these patients is suggested. However, further studies on this field are needed.

Al-Yahya et al. demonstrated that oral administration of the methanolic extract of *Boswellia sacra* for 28 days did not cause any significant toxicity to the kidney and liver up to doses of 100 mg/kg in rats (Al-Yahya, Asad, Sadaby, & Alhussaini, 2020). The safety of acute oral administration of the ethanolic extract at a dose of 5,000 mg/kg and the crude extract of *Cyperus rotundus* at a dose of 2000 mg/kg, as well as sub-acute administration of the ethanolic extract at a dose of 500 mg/kg was confirmed in rats (Pirzada et al., 2015). In the study of *Mubarak Iminjan* et al., the acute toxic effects of *Quercus infectoria* aqueous extract on mice were investigated, and no side effects were observed up to a dose of 10 g/kg. Furthermore, the chronic toxic effects of *Q. infectoria* on rats at a dose of 0.2–2 g/kg were examined, and no side effects were evident for up to 180 days of the study (Iminjan et al., 2014). The standard dose of *Saussurea costus* is 3 g/day (Hempen & Fischer, 2009). It was demonstrated that the oral administration of the ethanolic extract of *S. costus* exerts protective effects against paracetamol-induced toxicity on the liver and reproductive system at a dose of 300 mg/kg for 14 days in rabbits (Kadhem & Kadhum, 2019). No acute toxic effects were observed for *Piper longum* up to a dose of 3 g/kg in rats, and chronic toxicity studies for 90 days revealed no adverse effects (Kumar, Kamboj, & Suman, & Sharma, S., 2011). *Piper nigrum* is safe for therapeutic use up to a dose of 1.5 g/day (Thomson PDR Staff, 2004). *Zingiber officinale* is considered safe by the United States Food and Drug Administration (FDA) up to a daily dosage of 4 g (Ryan & Morrow, 2010). In the present study, the administration of FHP for 4 weeks led to no significant changes in the values of blood parameters including BUN, creatinine, SGOT, SGPT, ALP, total and direct bilirubin, and CBC. Considering that urinary incontinence in elderly patients may be a chronic problem that requires long-term medication, the current study cannot show the long-term toxic effects of FHP.

TABLE 5 Mean outcome measures between the three groups before the treatment and at weeks 2, 4, and 6

Variable[a]		Time				*p*-value[b]		
		Baseline	Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
Frequency of urinary incontinence	Group 1	3.84 ± 0.13	2.63 ± 0.21	2.33 ± 0.21	2.58 ± 0.23	<0.001***	<0.001***	<0.001***
	Group 2	3.70 ± 0.13	2.82 ± 0.22	2.71 ± 0.24	3.32 ± 0.19	<0.001***	<0.001***	0.01*
	Group 3	3.61 ± 0.14	3.23 ± 0.19	3.38 ± 0.16	3.55 ± 0.16	0.10	0.08	0.66
	p-value[c]	0.20	0.12	0.002** Group 1 vs 3: <0.001*** Group 2 vs 3:0.04* Group 1 vs 2:0.23	0.004** Group 1 vs 3:0.002** Group 2 vs 3:0.47 Group 1 vs 2:0.01*			
Amount of urine leakage	Group 1	3.84 ± 0.34	2.27 ± 0.34	1.78 ± 0.32	1.96 ± 0.33	<0.001***	<0.001***	<0.001***
	Group 2	3.61 ± 0.30	2.55 ± 0.32	1.91 ± 0.27	3.08 ± 0.30	0.004**	<0.001***	0.04*
	Group 3	3.20 ± 0.32	3.11 ± 0.33	3.20 ± 0.32	3.14 ± 0.31	0.41	0.99	0.31
	p-value[c]	0.34	0.16	<0.001*** Group 1 vs 3:0.002** Group 2 vs 3:0.004** Group 1 vs 2:0.37	0.01* Group 1 vs 3:0.008** Group 2 vs 3:0.88 Group 1 vs 2:0.009**			
Score of urinary incontinence	Group 1	14.60 ± 0.67	9.39 ± 0.78	7.75 ± 0.83	8.75 ± 0.94	<0.001***	<0.001***	<0.001***
	Group 2	14.20 ± 0.59	10.88 ± 0.86	10.02 ± 0.85	12.82 ± 0.77	<0.001***	<0.001***	0.01*
	Group 3	12.82 ± 0.65	11.91 ± 0.73	12.14 ± 0.74	12.47 ± 0.69	0.56	0.98	0.48
	p-value[c]	0.14	0.07	<0.001*** Group 1 vs 3: <0.001*** Group 2 vs 3:0.06 Group 1 vs 2:0.06	<0.001*** Group 1 vs 3:0.001** Group 2 vs 3:0.76 Group 1 vs 2:0.002**			
Quality of life	Group 1	70.55 ± 2.29	56.73 ± 2.85	51.70 ± 2.93	55.91 ± 3.41	<0.001***	<0.001***	<0.001***
	Group 2	69.88 ± 2.69	61.88 ± 2.90	61.82 ± 3.01	66.56 ± 2.97	0.001**	0.002**	0.07
	Group 3	63.12 ± 2.93	61.97 ± 2.85	62.79 ± 2.95	63.18 ± 2.98	0.18	0.82	0.61
	p-value[c]	0.12	0.34	0.01* Group 1 vs 3:0.005** Group 2 vs 3:0.90 Group 1 vs 2:0.01*	0.03* Group 1 vs 3:0.06 Group 2 vs 3:0.42 Group 1 vs 2:0.01*			

[a]Data are presented as Mean ± SEM;
[b]Within group comparison (compared to the baseline);
[c]Between group comparison; Group 1: frankincense-based herbal product, Group 2: solifenacin, Group 3: placebo.
*p-value < .05; **p-value < .01; ***p-value < .001.

In addition to pharmacological and surgical treatments, conservative management methods including behavioral and physical therapy are also effective in reducing the symptoms of stress or urge urinary incontinence (Balk et al., 2019; Tran & Puckett, 2022). Therefore, in the present study, patients who received any conservative treatment were excluded from the study.

This study had also some limitations. One of the limitations of this study is that the present study is a monocentric study, in which duration of intervention and follow-up was short term, and the study was conducted in postmenopausal women. It is necessary to carry out studies with a longer treatment and follow-up duration to investigate the possible toxic effects of FHP since there are several compounds in FHP that, not only in isolation but mainly in combination with each other, may have deleterious effects on health, which were not observed in this study. The present study was conducted on mixed urinary incontinence, which is the most common type of urinary incontinence. Therefore, another limitation of the current study is the selection of a large field of mixed urinary incontinence; hence, it is suggested that the effect of FHP on other types of urinary incontinence such as stress and urge incontinence should be investigated in future studies. In addition, further studies on men and premenopausal women are suggested.

According to the results of this study, FHP has a similar efficacy in reducing the symptoms of urinary incontinence as the standard drug—solifenacin—and could improve the QOL in patients during the study period. Furthermore, after discontinuation of the drug, more lasting effect of FHP was significant compared to solifenacin. Therefore, FHP can be considered as a complementary treatment option to treat and reduce the symptoms in women with MUI. However, further studies are needed to better judge the results by overcoming the limitations of the present study.

ACKNOWLEDGMENTS

This study is based on a PhD thesis by Mahbubeh Karbalaiee and it was funded by a grant from Kerman University of Medical Sciences, Kerman, Iran (No: 97000624).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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How to cite this article: Karbalaiee, M., Daneshpajooh, A., Khanjani, N., Sohbati, S., Mehrabani, M., Mehrbani, M., & Mehrabani, M. (2022). Efficacy of frankincense-based herbal product in urinary incontinence: A randomized, double-blind, placebo- and active-controlled clinical trial. *Phytotherapy Research*, 1–17. https://doi.org/10.1002/ptr.7691