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ORIGINAL ARTICLE

Safety and efficacy of a class II medical device based on highly purified and standardized plant extracts in the management of post-menopausal patients with vulvar and vaginal atrophy: a single-center prospective observational study

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ABSTRACT

BACKGROUND: Despite the gold standard treatment for genitourinary syndrome of menopause (GSM) is based on the use of local or systemic estrogen-containing products, the typical long-term side effects of hormonal treatments and, most importantly, the contraindications in patients with history of breast and endometrial neoplasms do limit in some extent its use. As hyaluronic acid and some highly purified botanicals have clearly demonstrated their anti-inflammatory and mucosa-protecting properties, we have tested, in women with GSM, a class II vaginal medical device containing hyaluronate gel and a mucoadhesive active enriched with purified alkylamides from *Zanthoxylum bungeanum*, triterpenes from *Centella asiatica* and high molecular weight polysaccharides from *Tamarindus indica*.

METHODS: Our single-center, open-label, prospective and observational study was conducted on 50 menopausal women enrolled at the Department of Maternal-Fetal Medicine at Umberto I Polyclinic Hospital in Rome, Italy. Gel administration lasted 150 days and was performed daily for the first 12 days and every 48 hours for the remaining 138 days. Clinical evaluations were performed at baseline and after 12, 57 and 150 days. Besides product safety, main outcomes of our study were: 1) vaginal health (by Vaginal Health Index score [VHI]); 2) sexual quality of life (by Female Sexual Distress Scale [FSDS]); and 3) percentage of women declaring regular sexual activity.

RESULTS: The product was safe with no specific adverse events reported. It significantly improved VHI (about 5% after 57 days and 8% after 150 days), FSDS (about 7% after 57 days and 10% after 150 days), and sexual activity (about 20% after 150 days). It also reduced dryness, dyspareunia, burning, itching, and dysuria incidence, respectively by about 18%, 14%, 14%, 27% and 11% after 150 days.

CONCLUSIONS: In women with GSM, the intravaginal administration of a hyaluronate-based gel enriched with purified botanical actives endowed with anti-inflammatory and mucosal-protecting properties, reduced painful sensation during sexual acts and increased regular sexual activity.

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KEY WORDS: Menopause; Dyspareunia; Dysuria.

Genitourinary syndrome of menopause (GSM) is a chronic and progressive syndrome characterized by a collection of genital and urinary signs and symptoms secondary to the state of hypoestrogenism related to menopause. Previously known as vulvovaginal atrophy (VVA), in 2014 the International Society for the Study of Women's Sexual Health introduced a new terminology to describe this frequent and bothersome syndrome, to stress its dual nature (genital and urinary) and include all the signs and symptoms experienced by post-menopausal women affected by this condition.[1] GSM is a frequent disorder in menopause with an estimated prevalence of vaginal dryness up to 85% of women over 40 years of age with an additional 29-59% reporting dyspareunia and another 33-77% reporting vaginal itching and irritation.[2-4] These symptoms were proved to have a direct association and an important effect on the quality of life of post-menopausal women.[5] During menopause, the decrease of circulating estrogens and the modification of the estrogen receptors expression pattern, lead respectively to a reduction in vaginal lubrication and thinning of the vaginal and vulvar mucosa, which become less elastic and frailer.[6] Estrogens deficiency also leads to the reduction of dermal collagen in the dense connective tissue of vagina, bladder, and urethra, causing the vaginal wall to become less elastic and thinner and determining a shortening and a narrowing of the vagina, which may lead to dyspareunia. In addition, the decrease in local blood flow, the progressive reduction in vulvar Langerhans cells and the increase of vaginal pH (secondary to the gradual reduction of vaginal *Lactobacillus* spp.), result in the progressive decay of cell-mediated immunity and the overgrowth of Gram-negative rod fecal flora, exposing the patients to recurrent urinary tract infections (UTIs) and vaginitis.[6-10]

GSM severely impacts on woman life. A recent survey conducted on 3520 postmenopausal women from six countries reported that 45% of subjects have experienced vaginal symptoms and 75% have stated that their symptoms had a negative impact on life.[11] A similar study, conducted on 500 American women, highlighted that about 50% of them reported vaginal discomfort, and the most frequent symptoms were vaginal dryness and pain during intercourse.[12] Likewise, the same research described several events related to vaginal discomfort: negative impact on their lives (80%), adverse effect on sexual intimacy (75%), feeling less sexual (68%), negative consequences on marriage (33%) and on self-esteem (26%).[13] As well-known, if untreated, genitourinary syndrome is progressive and worsen sexual function and quality of life.[14, 15] Despite menopausal women well-recognize genitourinary syndrome as a chronic condition, they are anyway reluctant to discuss with their physician about their vaginal or sexual discomfort. The main reasons for this reluctance can be traced back to shame, embarrassment, concern about the side effects of treatment or distrust of a precise identification of the problem.[4] The main impediments to get a correct identification of genitourinary syndrome and to identify the appropriate treatment include limited time during patient visit, lack of physician training regarding the diagnosis and treatment of this condition, and the misconception that genitourinary syndrome only affects sexually active women.[16]

Historically, the gold standard treatment for this syndrome was based on local or systemic estrogens-containing products, but it was burdened with the typical long-term side effects of hormonal treatments and, most importantly, it is contraindicated in patients with history of breast and endometrial neoplasms.[17-21] The safer alternative to hormonal treatments is represented by locally acting non-hormonal therapeutic strategies. To date, they represent likely the most prescribed products for the GSM treatment.

Zantogin® Gel ([ZG] Labomar SpA, Istrana, Treviso, Italy) is a multicomponent vaginal lubricant (for formula details see the "Materials and methods" section), endowed with lenitive and anti-inflammatory properties, developed as class II medical device for the treatment of VVA. As other studies have already shown the efficacy of ZG in controlling and preventing relapses of symptoms such as vulvar burning and itching,[22] the aim of our prospective, observational study was to evaluate the efficacy and safety of ZG in the treatment of post-menopausal VVA signs and symptoms, in terms of improvement of objective parameters assessing vaginal health, measured by the Vaginal Health Index (VHI) score and patients' sexual

quality of life, measured by the Female Sexual Distress Scale (FSDS) and by the recovery of a regular sexual activity.[23, 24]

Materials and methods

Tested product

Zantogin® Gel (ZG, Labomar SpA) is a class II medical device, intended for intravaginal use. ZG is a gel containing as main actives: hyaluronate (0.5%), Zanthalene® (0.5%), *Centella asiatica* selected triterpenes Phytosome® (1%), Xilogel® (1%) and Polycarbophil® (0.8%). Hyaluronate was purchased from Givaudan SA (Vernier, Switzerland) and its chemical-physical features are described in Supplementary Digital Material 1 (Supplementary Text File 1). Zanthalene® (Indena S.p.A., Milan, Italy) is an Ecocert validated CO_2 extract obtained from the fruit husks of *Zanthoxylum bungeanum*. It is characterized by the standardized profile of lipophilic alkylamides known as hydroxy α-, β- and γ-sanshools. Its chemical-physical features are described in Supplementary Digital Material 2 (Supplementary Text File 2). *Centella asiatica* selected triterpenes Phytosome® was purchased from Indena S.p.A. The product, obtained by hydro-ethanolic extraction from *Centella asiatica* leaves (Supplementary Digital Material 3: Supplementary Text File 3), was standardized to contain, in weight, 1/3 of triterpenes (asiatic acid, madecassic acid and asiaticoside) and 2/3 of distearoylphosphatidylcholine form sunflower. As a marker, the percentage of asiaticoside in the Phytosome® formulation, analyzed by HPLC, was 13.8% according to ARM/79-8031. Xilogel® (Indena S.p.A.) is a well characterized high molecular weight polysaccharide mixture obtained from hydro-ethanolic extraction from the seed of tamarind. Xilogel® (Indena S.p.A.) chemical-physical features are described in Supplementary Digital Material 4 (Supplementary Text File 4). Polycarbophil® is a mucoadhesive polymer purchased from Lubrizol Corporation (Wickliffe, OH, USA) which chemical-physical features are described in Supplementary Digital Material 5 (Supplementary Text File 5). The full class II medical device dossier (N. 1249801) was deposited at the Italian health authorities and its latest revision was done in 2020.

Ethical considerations

The trial is a single-center, prospective, observational study conducted at the Department of Maternal-Fetal Medicine at Umberto I Polyclinic Hospital in Rome, Italy. All data collection was performed within the Department from June 2021 to June 2022. The study has been conducted in accordance with the principles set forth in the Helsinki Declaration. Institutional review board approval was obtained by the Ethical Committee of Sapienza University (Rome, Italy) *via* document number 6407 released on June 9, 2021. The trial was registered on www.clinicaltrials.gov with identifier number as NCT05871255. Participants were given oral and written information, and each of them signed an informed consent form. The personal data were managed in compliance with the Privacy as per EU Regulation 2016/679 by registering only the initials of the name and surname, made anonymous based on a reserved coding. All patients were assured that declining to participate in the study or leaving the study at any point would not affect the quality of their treatment and that they would thereafter receive the best care available.

Inclusion criteria and exclusion criteria

Inclusion criteria were: 1) age between 45-65 years and sexually active; 2) Eastern Cooperative Oncology Group performance status of 0 or 1;[25] 3) menopause and symptomatic (vaginal dryness, dyspareunia, vaginal irritation, vaginal itching, dysuria) vulvovaginal atrophy (VVA); 4) no previous treatment for VVA; and 5) informed consent signed. Exclusion criteria were: 1) state of pregnancy; 2) abnormal genital bleeding or vaginal infection; 3) previous or concurrent neoplasms; 4) uncompensated concomitant diseases (*i.e.*, diabetes, cardiac diseases); and 5) previous or concurrent HRT or radiotherapy or chemotherapy.

Outcomes and protocol

Outcomes of our study were the evaluation of: 1) product safety; 2) vaginal health (by Vaginal Health Index score); 3) sexual quality of life (by Female Sexual Distress Scale [FSDS]); and 4) percent of women declaring the recovery of

a regular sexual activity. The investigators also collected the patients' subjective score concerning vaginal dryness, dyspareunia, burning and itching, and dysuria.

The enrolled patients applied the vaginal gel (ZG) for a total of 150 days of treatment. It was performed daily for the first 12 days, and every 48 hours for the remaining 138 days (that is until the end of the study). No interruption of treatment has been reported. Patients were examined at the enrollment (T0), and after 12 (T1), 57 (T2) and 150 (T3) days of treatment. Examination included: 1) the filling of a Female Sexual Distress Scale (FSDS) Questionnaire; and 2) a gynecological examination with colposcopy and pH test to evaluate vaginal elasticity, vaginal secretions, pH, mucosal epithelium, and vaginal hydration to calculate the VHI. The VHI was obtained by adding the score (from 1 to 5) of each of the five parameters considered. We have classified therefore as poor vaginal health a VHI corresponding to 5 and a normal vaginal health with a VHI corresponding to 25. The FSFD questionnaire (Table I) includes 13 questions, investigating how often the patient suffers about her sexual life. The resulting score corresponds to the sum of the weighted answers for each item: a score of ≥11 effectively discriminates between women with FSD and women without FSD.

TABLE I.—*FSDS (Female Sexual Distress Scale) questionnaire.*

Variable	Score				
How often do you feel					
Distressed about your sex life	0	1	2	3	4
Unhappy about your sexual relationship	0	1	2	3	4
Guilty about sexual difficulties	0	1	2	3	4
Frustrated by your sexual problems	0	1	2	3	4
Stressed about sex	0	1	2	3	4
Inferior because of sexual problems	0	1	2	3	4
Worried about sex	0	1	2	3	4
Sexually inadequate	0	1	2	3	4
Regrets about your sexuality	0	1	2	3	4
Embarrassed about sexual problems	0	1	2	3	4
Dissatisfied with your sex life	0	1	2	3	4
Angry about your sex life	0	1	2	3	4
Bothered by low sexual desire	0	1	2	3	4

The FSDS questionnaire includes 13 questions, investigating how often the patient suffers about her sexual life. The resulting score corresponds to the sum of the weighted answers for each item: a score of ≥11 effectively discriminates between women with FSD and women without FSD.
0: never; 1: rarely; 2: occasionally; 3: frequently; 4: always.

Adverse events collection procedures

Adverse events (AE) could be reported directly from the enrolled patient or be discovered by medical staff during the performance of a physical examination. In both cases, the investigator documents the nature of the AE, the date of onset, its severity, assessing also the possible causal link between the AE and the medical device as previously described.[26]

Sample size estimation and statistical analysis

The mean VHI in patients affected by vulvovaginal atrophy is equal to 10.58±1.71.[27] We expected to identify at least a 13.2% change in the mean VHI value in the affected population, setting $\alpha = 0.05$ and power = 0.80.[28] A minimal sample size, N.=14, was then determined by using the free software available on www.biomath.info. As our department registers reported, in the five past years, a minimum number of menopausal patients affected by VVA corresponding to 30 per year, so we assumed to enroll at least this number of patients to detect significant changes in VHI. From a statistic perspective, our aim was to compare four samples of patients respectively named: X={X1, X2, …, X50}, where *X* represents the screening visit at T0; Y={Y1, Y2, …, Y50}, where *Y* represents the visit to T12; W={W1, W2, …, W50}, where *W* represents the visit to T57; and Z={Z1, Z2, …, Z50}, where *Z* represents the visit to T150. X, Y, W, Z represent therefore the values of the VHI of the i^{-th} subject in the corresponding visits.

Statistical analysis

To observe whether the analyzed four populations could be represented by the same distribution (demonstration of the ineffectiveness of the treatment) or from different distributions (in this last case, to verify the effectiveness of the treatment, the test on variances on pair of samples or the analysis of the potential samples generated by the different distributions were needed), we assumed appropriate to use the following tests: 1) Welch's Parametric Test, generalization of Student's *t*-test, which is used for testing the hypothesis that two populations have equal means by assuming, in general, that the respective vari-

ances are not necessarily equal; 2) the non-parametric Wilcoxon-Mann-Whitney tests, to check whether two statistical samples come from the same population; 3) Kolmogorov-Smirnov Test + Fischer's Exact Test, to verify the "normality" of the samples and evaluate the hypothesis of equality between variances (in case the previous tests do not reject the hypothesis of equality between means). Based on the results of the tests, if the mean and variance of the first sample "do not result equal" to their respective counterparts in the second sample, further analyses, such as the comparison between "confidence intervals," provide us with the "measure of difference" between these quantities. Final data have been summarized using standard descriptive statistics. All calculated P values were 2-sided and P values<0.05 were considered statistically significant. All analyses were performed using the IBM-Microsoft SPSS version 25.0 for Windows (IBM, Armonk, NY, USA).

Results

From January 2022 to June 2022, a total of 50 patients were enrolled in the study. Patients' characteristics are shown in Table II. Briefly, the mean age was 58 years (range 46-65), the mean BMI was 27.4 kg/m² (range 22-34), previous hormonal tumors diagnosis was present in 10% of women (5/50), the median time from menopause to treatment was 5 years (range 2-8), previous pelvic surgery was evidenced in 22% of patients (11/50) and smoking habit was reported by 20% of patients (10/50). Patient's symptoms at T0 (baseline) and after 12, 57 and 150 days of treatment (T1, T2, T3) are shown in Table III and Figure 1. Evaluating the difference between T0 and T3, the incidence was reduced about by 18% for dryness, about 14% for dyspareunia, about 14% for burning, about 27% for itching and about 11% for dysuria. FSDS and VHI scores recorded at T0 (baseline) and respectively after 12, 57 and 150 days of treatment (T1, T2, T3) are shown in Table IV. After 12 days of treatment (T1), the perceived improvement was partial and not statistically significant being of -2.24% and +0.82% respectively for FSDS and VHI. Significant improvements were observed at T2, both in the subjective evaluation of the FSDS (-7.24%; P<0.001) and with the objective evaluation of the VHI (+4.94%; P<0.001). The improving trend of VVA-related signs and symptoms was then confirmed at T3 both for FSDS (-9.99%; P<0.001) and VHI (+8.07%; P<0.001). Regular sexual activity (Table IV) declared at T0 in 28 patients (56%) and at T3 in 34 patients (68%) showed a

TABLE II.—*Patients demographics and clinical characteristics.*

Parameters	Values
Age (y)	58.5±4.21
BMI (kg/m²)	27.4±2.85
Menopause (y)	5.78±1.87
Current smoker	10/50 (20%)
Previous hormonal tumors*	5/50 (10%)
Previous pelvic surgery	11/50 (22%)

Data are presented as mean±SD or as number of patients (%).
BMI: Body Mass Index; y: years.
*Endometrial or breast cancer.

TABLE III.—*Patient's symptoms at time 0 (T0, baseline) and after 12 (T1), 57 (T2) and 150 (T3) days of treatment.*

Parameters	T0 (baseline)	T1 (12 days)	T2 (57 days)	T3 (150 days)
Dryness	40 (80%)	38 (76%)	37 (74%)	33 (66%)
Dyspareunia	36 (72%)	36 (72%)	34 (68%)	31 (62%)
Burning sensation	28 (56%)	27 (54%)	25 (50%)	24 (48%)
Itching	15 (30%)	14 (28%)	12 (24%)	11 (22%)
Dysuria	9 (18%)	9 (18%)	8 (16%)	8 (16%)

Data are presented as number of patients. Into brackets is the % value of patients. The treated group was constituted by 50 patients.

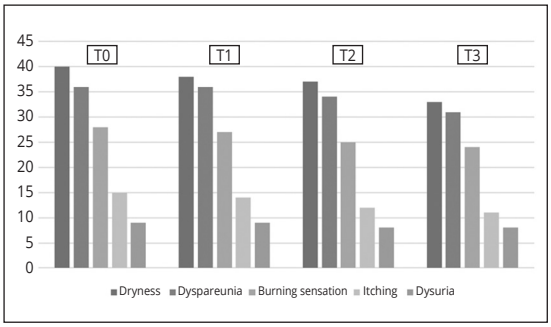

Figure 1.—Patient's symptoms at baseline (T0), and after 12 (T1), 57 (T2) and 150 (T3) days of treatment.
Figure shows a progressive and time-dependent symptoms reduction. Evaluating the difference between T1, T2 and T3 *versus* T0, the incidence was respectively reduced of about 5%, 7.5% and 18% for dryness, 0%, 6% and 14% for dyspareunia, 4%, 11% and 14% for burning, 7%, 20% and 27% for itching and 0%, 11% and 11% dysuria. Bars represent the number of patients affected by the symptom.

TABLE IV.—*FSDS, VHI and RSA.*

Parameters	T0 (baseline)	T1 (12 days)	P value	T2 (57 days)	P value	T3 (150 days)	P value
FSDS	19.62±3.533	19.18±3.224	0.132	18.20±2.878	<0.001	17.66±2.455	<0.001
VHI	12.14±1.959	12.24±1.733	0.255	12.74±1.291	<0.001	13.12±0.961	<0.001
RSA	28 (56%)	ND	–	ND	–	34 (68%)	<0.001

Data are presented as the mean±SD. For RSA the data are presented as number of patients. Into brackets is the % value of patients. Each statistic is calculated *versus* T0. The treated group was constituted by 50 patients.
FSDS: Female Sexual Distress Scale; VHI: Vaginal Health Index; RSA: regular sexual activity; ND: not done.

significant improvement (+21.43%; P<0.001). A clear improvement (data not shown) was also observed in vaginal pH reduction (T0: 5.5; T3: 4.5; P=0.004). Last, according to patients' reports, treatment adherence was very high (>95%; data not shown), the product was well tolerated and no adverse effects, related to the treatment, were reported throughout the observation period (data not shown).

Discussion

As demonstrated by the increased sexual activity and by the improved Quality of Life of patients, measured through well-known and standardized scores,[29, 30] our prospective study has clearly showed the safety and therapeutic efficacy of Zantogin® gel (ZG; Labomar SpA), a class II medical device, capable of exerting significant benefits on vulvar and vaginal signs and symptoms of GSM women. The data collected during the outpatient controls, after 12, 57 and 150 days from the beginning of the product application, express in numerical values such blessed effects and make our study, at least at our knowledge, the first clinical trial aimed to evaluate the soothing effect of vulvovaginal gels based on highly purified and pharmacologically active botanical extracts carried by hyaluronate. In our opinion, the reason for such an effect is likely due to the peculiar properties of the single active ingredients constituting the product formula.

Certainly, part of the global efficacy observed, at least that portion attributable to its purely mechanical role, is due to the well-known properties of hyaluronic acid. In ZG, this ingredient, which molecular weight is comprised between 1000 and 1400 KDa (Supplementary Text File 1), has been used as a carrier to spread and release locally the other active ingredients, but it likely cooperates in demonstrating their soothing properties. It is indeed known that hyaluronic acid is extremely polar. Thanks to this property, it binds water with high efficiency, conferring hydration, turgidity, plasticity, and viscosity to tissues and their surfaces, like in the case the vaginal mucosa. It also prevents damage to cells and tissue from physical and biological stress, thus acting as a lubricant. It then establishes direct interactions with the collagen fibers influencing aggregation and orientation as well as the ability to absorb shocks. Lastly, as it constitutes the largest polymeric net with which tissues and mucous membranes are equipped, it probably limits the spread of viruses and bacteria in the tissues.[31] Based on these mechanical properties, hyaluronic acid appears to be not only "a carrier" useful to formulate products to be used as alternative to non-hormonal treatments for counteracting the signs and symptoms of vaginal atrophy and dyspareunia, but also "an active principle" endowed with a possible effective role.[32] As previously said, hyaluronate is anyway an appropriate vehicle for active ingredients like those used to formulate the product we tested: Zanthalene® (Indena SpA) *Centella asiatica* selected triterpenes Phytosome®, Xilogel® (Indena SpA) and Polycarbophil® (Lubrizol Corporation).

Zanthalene® (Indena SpA) is a *Zanthoxylum bungeanum* highly purified extract standardized to contain some alkamides known for their therapeutic potential in the treatment of neuropathic pain, likely due to its CB_2-selective activity.[33, 34] This botanical used to obtain the extract, is a perennial plant of Chinese origin that grows in the Sichuan region.[35] In the traditional medicine, oily extracts from this plant are used to treat toothache and *Zanthoxylum bungeanum* is for this reason known as the "Toothache Tree". The fruits are used in the Chinese and Japanese

cuisine to moderate the pungent spices like peppers. Besides these effects, this botanical has a unique flavor and sensory properties, generating a lemony tingly dumbness, again due to the presence of their peculiar lipophilic alkamides, chemically indicated also as isobutylamides.[36] These last are easily extracted from *Zanthoxylum bungeanum* by using CO_2 in hypercritical conditions.[37] More precisely, the CO_2 extract of *Zanthoxylum bungeanum*, used to manufacture Zanthalene® (Indena SpA), is characterized by the presence of three different isobutylamides, respectively named α-, β-, and γ-hydroxysanshool.[38] Besides their role likely played on CB_2-receptors, these molecules are considered to interact with a yet undefined Na^+-dependent receptor causing the onset of action potentials that deplete the presynaptic neuron of neurotransmitter determining the absence of signal transmission. Due to that, preparations containing 0.5% of *Zanthoxylum bungeanum* extract (that is Zanthalene®, Indena SpA) are endowed with a clinically observed anti-itching and anti-burning effect.[39]

Centella asiatica selected triterpenes, also indicated as CAST, correspond to a highly purified mixture of three molecules respectively knows as asiaticoside (40%), asiatic acid (30%), and madecassic acid (30%). Their role is thought to be played mainly on fibroblast, promoting its ability and performance in synthetizing collagen. CAST mechanism of action clearly explains its role as a wound healer,[40, 41] and the Phytosome® formulation is known as a pharmaceutical strategy to promote the mucosal and skin delivery of actives from hydrogels.[42]

Xilogel® (Indena SpA) is a film-forming and moisture-regulating highly purified polysaccharides mixture obtained by extraction from *Tamarindus indica*. Chemically, they are branched polysaccharides having a cellulose-like molecular backbone (β-1-4-D-Glucose) mainly with xylose and galactoxylose branches. The molecular weight of these xiloglucans corresponds to approximately 650 KDa. These features make Xilogel® (Indena SpA) overlapping, in terms of functions, to human mucins and chemically endowed with muco-adhesive properties even superior to those characterizing hyaluronic acid. Due to that, their main clinical use is aimed to exert lenitive actions on inflamed mucous membranes.[43, 44] Finally, Polycarbophil®, is likely the most effective mucoadhesive polymer, capable of forming hydrogels on mucosa. For this reason, is commonly used to formulate vaginal drug delivery systems.[45]

The current gold standard for treating GSM are estrogen-based hormone therapies. However, numerous viable alternatives to estrogens have been proposed and their effectiveness demonstrated. Our group has conducted in the past several studies for the treatment of GSM demonstrating how the use of ospemifene and fractional CO_2 laser are valid alternatives for patients who refuse to take estrogen.[46-48] However, such methods are burdened by the hormonal nature of ospemifene and invasiveness for the execution of the laser procedure. In addition, both techniques require a prolonged use for the occurrence of beneficial effects and have also a transitional effect. The application of ZG is therefore another viable alternative to local or systemic estrogen therapy of VVA atrophy, especially for patients with history of estrogen-sensitive tumors, such as breast cancer and endometrial cancer.[49]

This study shows a significant effect of ZG on VVA atrophy. This is clearly displayed by the significant improvement of the total VHI and FSDS scores and by the increased restoration of a regular sexual activity. Noteworthy, despite not significant, the evident progressive trend of reduction in the incidence of the various GSM symptoms has, overall, contributed to determining an important global improvement in the patients' quality of life. It should be also noted that no patient reported any side effects after using the product for over 150 days. Although, apart from pH, we have not conducted analysis aimed at verifying the exact physiological mechanisms responsible for the observed improvements, our current assumption is that the improvement of symptoms could be likely due to: 1) an increase in the thickness of the vaginal mucosa; 2) a better lubrication during the sexual intercourse; 3) the neoformation of capillaries; 4) the consequent better tissue local spraying; 5) the reduction of friction; and 6) the normalization of

vaginal pH. In our opinion, thanks to the strict inclusion criteria and the careful enrollment of patients, this study has allowed us to validate the observed improvements as all attributable to the use of ZG.

Limitations of the study

Surely, this study is limited by the lack of a control group and by the consequent potential placebo effect. In addition, despite the significant results achieved, the number of patients included is likely too small to be able to draw definitive conclusions. For this reason, it is a purpose of our group to soon conduct larger, randomized, placebo-controlled trials to evaluate again the effects of ZG in patients with GSM.

Conclusions

Despite the above listed limitations, this trial should be considered useful being the only (or one of the few) study, to our knowledge, evaluating in a prospective manner the effects of a class II medical devices formulated with peculiar, highly purified, and standardized active ingredients obtained by extraction process from botanicals on sign and symptoms of GSM. In this trial the use of ZG has indeed significantly improved, without side effects, the quality of life in GSM symptomatic menopausal patients. Such patients, at the end of the treatment reported beneficial effects, as also demonstrated by the increased regular sexual activity, an important improvement in sexual desire, excitement, and ability to orgasm due to a better feeling of adequacy and the reduction of painful sensation during the sexual acts.

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Conflicts of interest

Francesco Di Pierro, Alexander Bertuccioli and Marco Monti are Pharmextracta consultants.

Authors' contributions

Valerio Galli and Marco Monti have given substantial contributions to study conception, Valerio Galli, Tullio Golia D'Augè, Amjad Khan, Giulia D'Ovidio, Francesco Iaculli, Valentina Tibaldi, Giusi Santangelo, Margherita Fischetti, Assunta F. Casorelli, Violante

Di Donato, Andrea Giannini, Angela Musella, Antonella Giancotti and Marco Monti to study design, Tullio Golia D'Augè and Marco Monti to study administration, Marco Monti to study supervision, Valerio Galli, Tullio Golia D'Augè, Francesco Di Pierro, Massimiliano Cazzaniga, Luigina Guasti, Nicola Zerbinati, Alexander Bertuccioli, Amjad Khan, Giulia D'Ovidio, Francesco Iaculli, Valentina Tibaldi, Giusi Santangelo, Margherita Fischetti, Assunta F. Casorelli, Violante Di Donato, Andrea Giannini, Angela Musella, Antonella Giancotti and Marco Monti to manuscript writing, revision and editing. All authors read and approved the final version of the manuscript.

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