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ORIGINAL ARTICLE

Assessing the Noninferiority of the Spermidine Hyaluronate Complex Relative to 17β-Estradiol Treatment in the Ovariectomized Murine Model of Vulvovaginal Atrophy

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Objectives: Vulvovaginal atrophy (VVA) presents significant challenges in postmenopausal women. VVA is typically managed either with hormonal-estrogenic therapy or nonpharmacologically with hyaluronic acid (HA) treatments. This study has investigated an advanced formulation, Ubigel Donna™, consisting of an spermidine hyaluronate (Spd-HA) complex formed by combining spermidine and HA. Initial clinical trials have demonstrated promising outcomes for this formulation.

Methods: Local administrations of Spd-HA gel, HA gel, and 17β-estradiol (E2) gel were evaluated under a pulsatile regimen in ovariectomized Wistar female rats for assessing therapeutic efficacy.

Results: While E2 treatment demonstrated robust tissue revitalization through restored endometrial thickness and estrus-like vaginal epithelia, the HA gel yielded contradicting atrophic conditions (metestrus). The Spd-HA gel demonstrated an intermediate mucosal status with enhanced differentiation. All three treatments demonstrated similar regulation of the vaginal pH.

Conclusions: This study reaffirmed the efficacy of the estrogen replacement therapy. More importantly, the Spd-HA approach can be considered as a promising alternative for patients unable to use hormonal treatments. Thus, Ubigel Donna™ can be considered as an enhanced nonpharmacological solution for the widespread burden of postmenopausal VVA.

Key Words: Estrogens, Hyaluronic acid, Polyamines, Postmenopause, Spermidine

INTRODUCTION

Postmenopausal and premenopausal women often experience hypoestrogenic conditions that can lead to vulvovaginal atrophy (VVA), a distressing genital condition characterized by morphological and functional alterations in the vaginal tissues [1]. These changes include thinning of the vaginal epithelium, predominance of parabasal cells, and reduced superficial cells, all indicative of estrogen deficiency [2]. Medical intervention is often required to relieve symptoms and improve genital health and quality of life [3].

Local estrogen therapy has traditionally been recognized and effective treatment for urogenital atrophy associated with VVA [4]. The efficacy of local estrogen preparations in managing VVA symptoms is well-established, with various estrogenic formulations showing comparable therapeutic benefits [4]. However, the precise mechanisms by which estrogen therapies influence the extracellular matrix composition of the hypoestrogenic vagina are not fully understood. Estrogen receptors (ERs) play a pivotal role in mediating these effects, including the stimulation of tight junctions in vaginal epithelial cells, as observed in studies using

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ovariectomized (OVX) rats treated with 17β-estradiol (E2) [5].

Hyaluronic acid (HA), a glycosaminoglycan abundant in healthy vaginal tissue, maintains tissue hydration and lubrication in the extracellular space of the submucosa [6]. HA-based gels have shown promise in alleviating vaginal dryness and dyspareunia by enhancing tissue hydration and reversing many vaginal issues associated with estrogen loss [6]. Although HA treatments can provide symptomatic relief, their long-term efficacy remains under debate [7]. Despite these benefits, doubts persist regarding the long-term efficacy of HA therapy for VVA [7].

A novel approach in the treatment of women's genitourinary syndromes involves an enhanced formulation of hyaluronan known as the spermidine hyaluronate (Spd-HA) complex, which combines spermidine (Spd) with HA. This complex has demonstrated potent trophic effects when locally administered, making it a promising therapeutic option for conditions like vulvodynia and potentially VVA [8,9].

This study uses an OVX murine model to assess the efficacy and safety of the Spd-HA complex, commercially known as Ubigel Donna™, in comparison to established therapies like local estrogen. The primary aim of this preclinical research is to demonstrate that Spd-HA is not inferior to local estrogen therapy in managing postmenopausal VVA. The HA treatment group is included not as a direct comparator to Spd-HA but to provide a reference point for the minimal effects of non-hormonal treatments and to illustrate the expected inferiority of HA compared to estrogen. This design allows us to focus on validating the effectiveness of Spd-HA relative to estrogen therapy while acknowledging the base effects of HA in the context of vaginal atrophy.

By assessing the potential of Spd-HA to address symptoms associated with VVA, this research seeks to contribute new insights into non-hormonal treatment options, filling a critical gap in available therapies for postmenopausal women who may not be suitable candidates for hormonal therapy.

MATERIALS AND METHODS

Experimental animals and protocol

All experiments were conducted before 2014 and adhered to the regulations that were in effect at the time, which did not mandate a specific ethical protocol for these experiments (see "Ethical standard"). The animals were managed by specialized personnel under the oversight of Veterinary Service inspectors. To minimize animal suffering, a limited group of OVX females (n = 10) was sourced from a specialized vendor (Charles River). Upon arrival, the OVX female Wistar HAN SPF rats at 6 weeks of age were housed in suspended Makrolon cages under controlled conditions: temperature maintained at 21.5°C ± 1.5°C, relative humidity at 55% ± 15%, with air exchange for 20 hours/day, and a 12-hour light-dark cycle. Throughout the study, rats had ad libitum access to tap water and commercial chow (Dottori Piccioni). The animals were acclimatized to these conditions for one week. Vaginal smears confirmed the absence of estrus phase, confirming successful ovariectomy and blockade of estrus.

After the acclimatization period, the animals were randomly assigned to experimental groups as detailed in "Treatment administration". Finally, the animals were euthanized under deep isoflurane anesthesia, and vaginal tissue was collected and fixed in 10% neutral buffered formalin. The formalin solution was prepared in-house as follows: 10 mL of 37% formaldehyde solution, 0.8 g NaCl, 0.4 g potassium phosphate monobasic, 0.65 g potassium phosphate dibasic, and 90 mL distilled water.

Ethical standard

All adopted procedures were in compliance with ethics committee and Italian Guidelines for Laboratory Animal Welfare. This study was conducted in full compliance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals and the general ethical principles for animal research outlined in the Strasbourg guidelines (1985). The Decreto Legislativo 26/2014, implementing Directive 2010/63/European Union on the protection of animals used for scientific purposes, which introduced more stringent ethical approval requirements, came into effect in March 2014. Prior to this, while regulations governing animal experimentation existed, formal ethical approvals or Institutional Review Board reviews were not standardized or required to the same extent. Nonetheless, all experiments were conducted following the guidelines and regulations applicable at that time, and in accordance with the institutional policies in place.

Treatment administration

Treatments were administered intravaginally using a sterile pipette. Each formulation (Spd-HA, E2, or HA)

was applied three times a week for four consecutive weeks, with a single daily application at the same time each day.

Phase 1: This phase involved five consecutive daily treatments.

Phase 2: Following Phase 1, Phase 2 consisted of a 5-day cycle followed by a 3-day cycle, mimicking a repeated therapy regimen similar to what might be used in human subjects. This design included a two-week off-dose period to monitor variations in the diestrus condition.

The details were reported in Table 1.

Investigational products

Spd-HA group: The concentration of Spd in the Spd-HA gel was informed by the study by Ghisalberti et al. [8], which demonstrated a reverse dose-related activity of Spd. Specifically, Spd at millimolar (mmol/L) concentrations was associated with growth inhibition, whereas micromolar (μmol/L) and nanomolar (nmol/L) concentrations led to stimulation of 30%–80% above basal levels. Based on these findings, we chose a 2% concentration of the Spd and high molecular weight hyaluronic acid (HMW-HA) complex, aiming to optimize efficacy while ensuring safety. Spd-HA complex, commercially known as Ubigel Donna™, manufactured by Tixupharma srl.

E2 group: The dosage of E2 was selected based on both in vivo experiments and clinical data concerning local estrogen treatments for VVA. We used Sandrena™, a commercial gel available in 1-g sachets with a concentration of 1.0 mg/mL of E2, along with excipients such as carbomer 934P, trolamine, propylene glycol, ethanol, and purified water. This concentration was chosen to reflect effective local estrogen therapy as used in clinical settings.

HA group: The HA group received a gel containing only HMW-HA without Spd. This group was used solely to establish a baseline for the effect of HA alone, rather than as a direct comparator with Spd-HA. The purpose was to demonstrate the threshold effect of HA and its inferiority compared to estrogen treatment. Hyaluronan (2%) provided by Esperis, was used in this study.

Histology

Vaginal samples were embedded in paraffin wax, sectioned into 2–3 micron thick slices, and stained with hematoxylin and eosin. For staining, Harris Hematoxylin solution was used followed by wash out in tap water. The slides were then briefly immersed in an alcoholic acid solution (70% ethanol and 1% hydrogen chloride) washed again with tap water, and stained with Eosin Y solution.

The samples were then dehydrated in ascending concentrations of ethanol: 70%, 95%, and 100%. The slides were immersed in Xylene. The substances used were purchased from Sigma Aldrich. Slices were mounted with a specific hydrophobic mounting medium (Bio-optica). The sections were examined and the related images were collected using an optical microscope (Olympus).

Histological and morphometric evaluations section – maturation index

Histological and morphometric evaluations of endometrial and mucosal structures were performed by a veterinary histopathology laboratory (Istovet di Luca Crippa & C). The grading was determined based on criteria outlined in Table 2, which included assessment of stratum mucification, stratum granulosum, stratum corneum, and stratum germinativum. The maturation index was calculated with OVX baseline = 1 and fertile condition = 3.

The evaluation of estrous cycle stages in mice is based on the known durations for each phase: proestrus (12–14 hours), estrus (25–27 hours), metestrus (6–8 hours), and diestrus (55–57 hours). While no standardized international grading system for these specific stages in murine models was identified in the literature, our approach utilizes these commonly reported cycle durations to derive an overall score for the estrous cycle. This method aligns with practices frequently used in experimental research to assess and quantify reproduc-

Table 1. Experimental setting with description of the groups under testing

Group	Experimental gel	n	Phase 1	Off-dose	Phase 2
HA	Hyaluronan, 2%	2	70 μL, 5 d	2 wk	150 μL, 5 + 3 d
E2	17β-estradiol gel, 1 mg/mL	4	30 μL, 5 d	2 wk	30 μL, 5 + 3 d
Spd-HA	Spermidine-HA, 1:10 eq/eq, 2%	4	70 μL, 5 d	2 wk	150 μL, 5 + 3 d

Table 2. Quali-quantitative assessment of the vaginal status

	Metaestrus	Diestrus	Proestrus	Estrus
Stratum mucification	Absent	Initial	Well developed	Absent
Stratum granulosum	Absent	Developing	Developing	Well developed
Stratum corneum	Reduced (3–4 cell layers) w/necrosis	Developing (5–6 to 8–10 cell layers)	Present	Well developed (8–10 cell layers)
Stratum germinativum	Absent	Attenuated	Present	Present
Neutrophyl infiltration	Many	Few	Rare	Few
Vaginal score	1	2	2.5	3

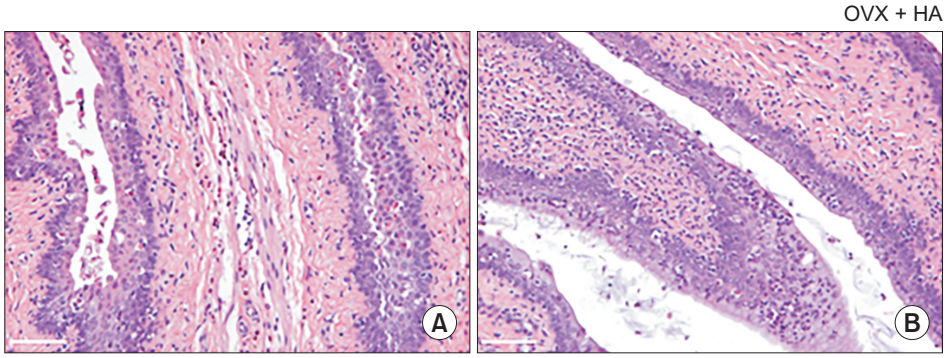

Fig. 1. Impact of hyaluronic acid (HA) treatment on ovariectomized (OVX) vaginal mucosa. (A, B) The 2 animals in the HA group showed a reduced vaginal mucosa consisting of 3 to 4 cell layers, with rare neutrophils and a variable number of necrotic cells. Stratum mucification, stratum corneum, and stratum granulosum were absent, indicative of a luteinic phase, i.e., a metestrus or anestrus-equivalent stage (H&E, ×40). Scale bar: 50 μm.

tive cycle stages.

Score definitions

Baseline = 1: Metestrus phase, characterized by a reduced germinal layer (3–4 cell layers) with the absence of mucinous, granular, and cornified layers. There is a presence of some polymorphonuclear cells and variable necrotic cells.

Intermediate = 2/2.5: Diestrus/proestrus phase, marked by an increased germinal layer (8–10 cell layers) but still lacking the granular and cornified layers.

Fertile condition = 3: Estrus phase, where the mucosal layer is fully developed, with a complete germinal layer covered by well-formed granular and cornified layers.

pH vaginal measurements

In vivo vaginal pH was measured using pH indicator strip before and after treatment in each experimental group. The vaginal score reflects the impact of murine ovariectomy on cell survival, apoptosis, and endometrial atrophy, consistent with findings from previous studies on the OVX model [10,11].

Statistical analysis

All data were expressed as mean ± standard error of the mean (M ± SEM). We analyzed the data using JASP (an open-source software developed by the University of Amsterdam), a free and user-friendly statistical software. For our analysis, we employed *t* test or multiple *t* tests paired to evaluate the differences between 2 groups or before/after the treatments. Given the preliminary nature of these experiments and the concurrent initiation of a clinical pilot study in women, we intentionally limited the number of animals used. This decision was made to adhere to ethical standards aimed at reducing animal suffering. These pilot data provide a valuable foundation for our research, allowing us to transition to human studies without unnecessarily increasing the number of animal subjects. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Vaginal epithelial changes in response to treatments

The mucosa of the HA group exhibited an atrophic condition similar to metestrus, characterized by a pre-

dominance of basal and parabasal cells with a complete absence of intermediate, superficial (cornified) cells, or leukocytes, indicative of the luteal phase (Fig. 1). In contrast, the E2 group demonstrated a fully restored trophic condition, marked by the absence of basal and parabasal cells, and a predominance of intermediate and superficial cells along with leukocytes, typical of the estrus stage (Fig. 2). The Spd-HA group displayed a range of trophic responses, including an atrophic state with predominant basal and parabasal cells, minimal intermediate cells, and no superficial (cornified) cells or leukocytes (Fig. 3A and 3B); an intermediate trophic status with few basal and parabasal cells, predominant intermediate cells, and no superficial cells or leuko-

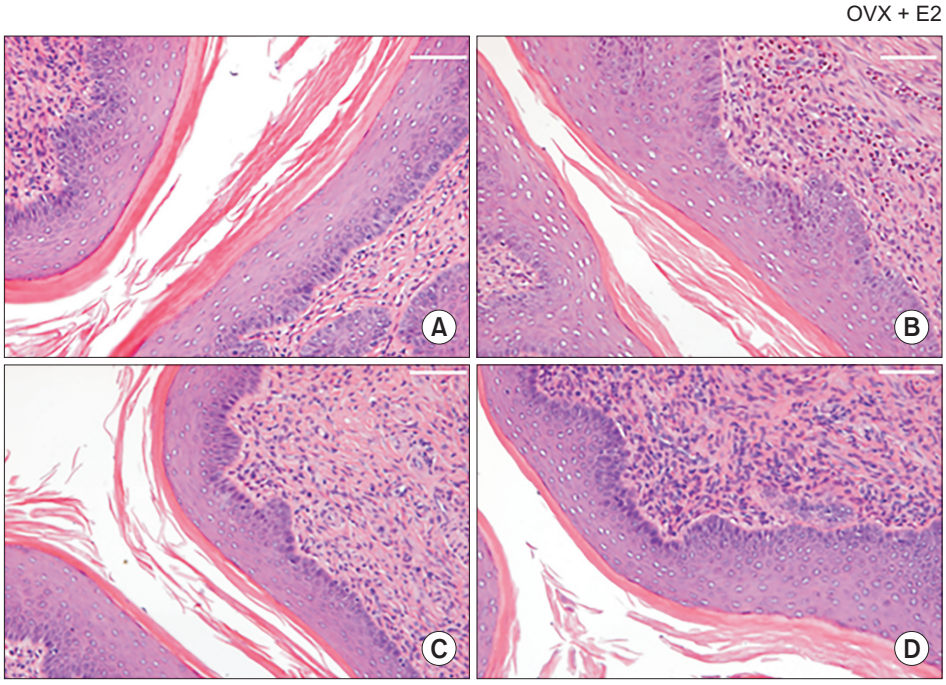

Fig. 2. Impact of 17β-estradiol (E2) treatment on ovariectomized (OVX) vaginal mucosa. The 4 animals in the E2 group (A–D) exhibited hyperplastic vaginal mucosa with a full stratum germinativum consisting of 8–10 layers. The stratum granulosum and stratum corneum were well-developed, resembling an estrus condition (H&E, ×40). Scale bar: 50 μm.

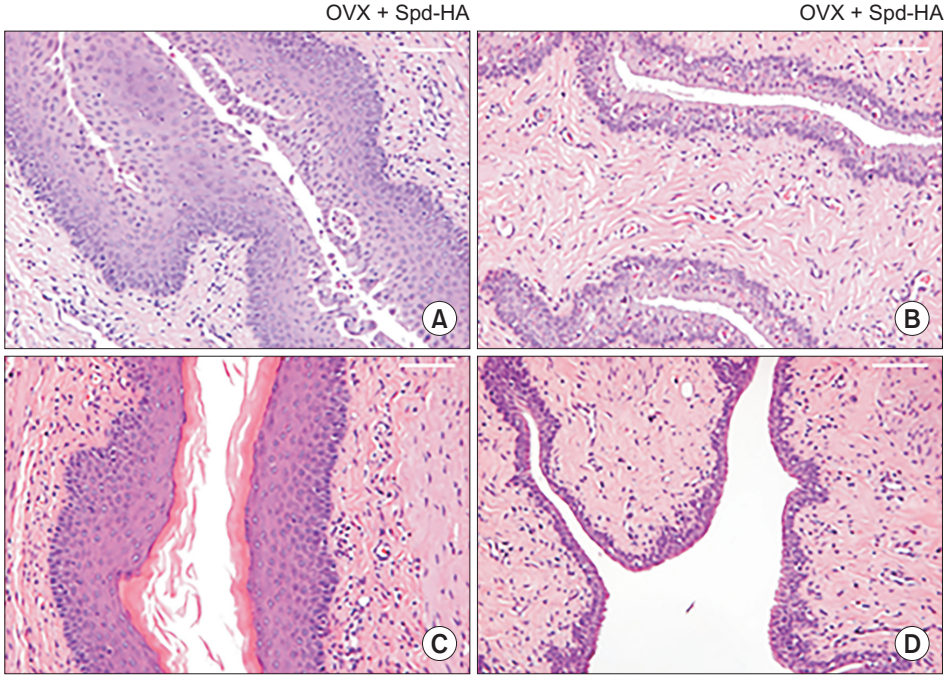

Fig. 3. Impact of spermidine hyaluronate (Spd-HA) treatment on vaginal mucosa of ovariectomized (OVX) rats. This group exhibited varied and scattered features. (A, B) In these 2 animals mucosae showed hypoplastic vaginal mucosa similar to that of hyaluronic acid-treated animals, indicative of a luteinic phase (metestrus). (C) In the third animals' mucosa displayed signs of early proliferation and regeneration, with the stratum germinativum increasing to 8–10 layers, though the stratum spinosum and stratum corneum were absent, indicating diestrus. (D) In the fourth animal mucosa presented hyperplastic features, with a stratum germinativum of 8–10 layers, and well-developed stratum granulosum and stratum corneum, typical of the follicular phase (estrus) (H&E, ×40). Scale bar: 50 μm.

cytes, indicating early proliferation and regeneration (Fig. 3C); and a fully trophic condition with predominant intermediate and superficial cells and the presence of leukocytes, resembling a hyperplastic state similar to the follicular phase (Fig. 3D). Morphologically, the HA group had fewer crypts in the vaginal mucosa (Fig. 1), while the E2 group showed significant signs of proliferation, including mitosis and stratification, and a greater number of crypts in the lamina propria (Fig. 2). In the Spd-HA group, two rats showed more pronounced proliferation compared to the HA group, with areas of stratified columnar epithelium (Fig. 3A and 3C), while the other two rats exhibited a mucosal pattern similar to the HA group (Fig. 3B and 3D).

Histological evaluation of epithelial and endometrial thickness

When we measured the vaginal epithelial thickness it just showed a trend in amelioration in E2 and Spd-HA groups compare to HA alone without significant statistical differences. In contrast, the endometrial thickness was significantly increased with hormone treatment and exhibited a similar trend with Spd complex treatment (Fig. 4).

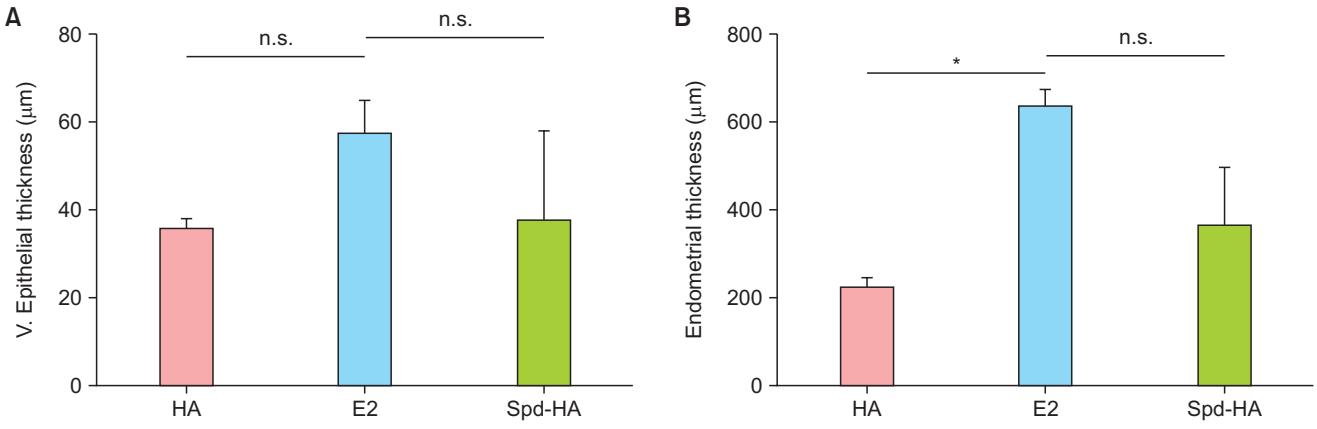

Fig. 4. Impact of treatments on tissues thickness. (A) On vaginal epithelium thickness and (B) endometrial thickness in spermidine hyaluronate (Spd-HA), 17β-estradiol (E2), and hyaluronic acid (HA) groups. Statistical significance was calculated using *t* test. Data are presented as the mean ± standard error of the mean. n.s.: not significant. *$P < 0.05$.

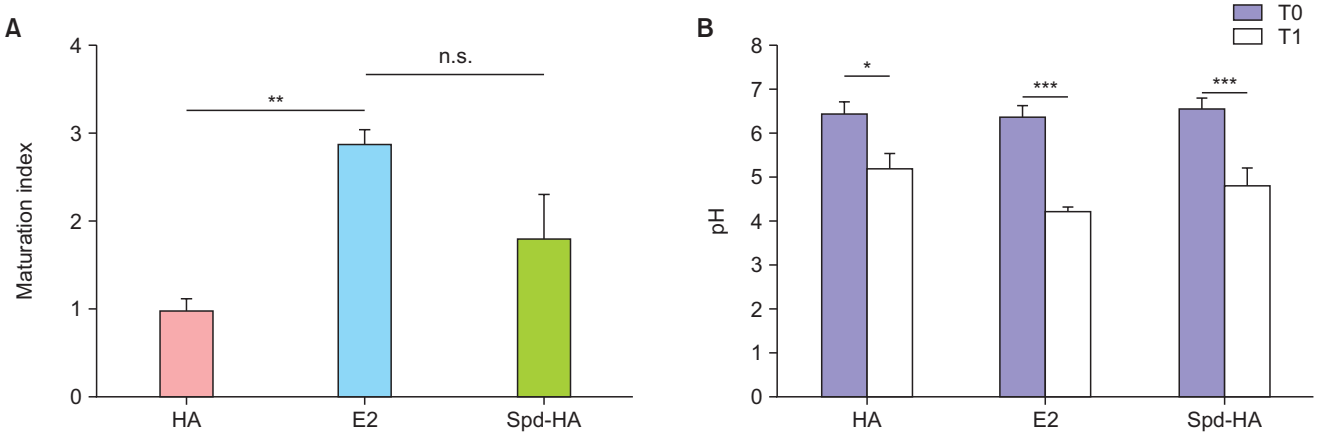

Fig. 5. Effect of treatments on maturation index and pH. (A) Maturation index reveals minimal impact with hyaluronic acid (HA) treatment, restored multiple-layered epithelium with 17β-estradiol (E2), and intermediate effects with spermidine hyaluronate (Spd-HA). Statistical significance was calculated using one way analysis of variance. (B) Changes in vaginal pH before (black bars) and after treatment (white bars) in HA, E2, and Spd-HA groups. Statistical significance was calculated using multiple *t* test paired. Data are presented as mean ± standard error of the mean. n.s.: not significant. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Quantitative assessment of vaginal status

A quali-quantitative assessment of the vaginal status calculated according to criteria in Table 2 is depicted in Figure 5A. The maturation index, which evaluates the progression of vaginal epithelial maturity, showed that HA had the lowest score, which was significantly different compared to the E2 treatment. The Spd-HA treatment resulted in a higher maturation index compared to HA alone and was not significantly different from E2. All treatments ameliorated the vaginal homeostasis partially restoring the altered, high pH milieu of OVX vaginas, although at different extents, as set forth in Figure 5B.

DISCUSSION

Our study employed the OVX rat model to assess Spd-HA gel as a potential therapy for VVA. This model effectively mimics the hypoestrogenic state observed in postmenopausal women, resulting in significant alterations in the reproductive tract [12,13]. Known phenotypic changes in this model include a decreased uterine-to-body weight ratio despite no significant change in total body weight. Vaginal tissues post-ovariectomy exhibit atrophic characteristics, including epithelial thinning, mucosal changes, and altered pH. This hypoestrogenic environment disrupts the integrity of the female urogenital tract, compromising factors like epithelial thickness, vaginal smooth muscle density, and vascular and neuronal architecture [12,13]. This study is of particular significance given the challenges of obtaining comparable control groups in human studies across various treatments. Moreover, ethical and practical constraints limit the analysis of post-treatment biopsies in women. Thus, our study provides valuable insights in the design and understanding of next clinical trials.

In our experiments, we evaluated the effects of vaginally administered Spd-HA gel, HA, and E2 gels on the vaginal tissues of OVX Wistar female rats. E2 and HA are commonly used treatments for managing local symptoms of VVA [10,11,14]. The E2 group significantly improved endometrial thickness, closely resembling intact non-OVX tissues. In contrast, HA treatment had minimal impact on the atrophic condition, while Spd-HA treatment afforded intermediate improvements. Distinctions emerge in endometrial status, where the E2 group showed deep ER-mediated effects, and Spd-HA displayed marked efficacy. These findings underscore the potential of Spd-HA, highlighting its therapeutic promise in the treatment of VVA.

Across all conditions, we noted a positive change in pH levels. In pre-menopausal women, ovarian hormones facilitate the proliferation of Doderlein lactobacilli, which metabolize glycogen to produce lactic acid. This conversion is crucial for sustaining vaginal acidity, thereby maintaining a normal pH level between 4.0 and 5.0 during the active phases of the menstrual cycle [15]. In rodents, the pH level in the proestrus phase is 5.57 and decreases to 4.53 in the estrus phase. The vaginal epithelial pH, initially the same across all groups (higher than 6), was significantly lowered in all treatment groups (lower than 5), indicating an improvement in vaginal health and restoration towards normal physiological conditions. This is important as a lower vaginal pH is associated with a healthy vaginal microbiome and reduced symptoms of VVA.

The morphology observed following treatments was more variable within the group in response to the Spd-HA compared to those in E2 or HA. This variability can be attributed to the extensive research and well-established dosing regimens of topical estrogens and HA, whereas research on Spd complexes is still relatively new. So far, studies have demonstrated its safety and efficacy across a range of concentrations and various dosages [8]. Preliminary data suggest that alternate-day administration is more effective than consecutive-day administration, as used in this study. Future research should explore the optimization of dosing schedules of Spd-HA to maximize therapeutic outcomes. Adjusting the administration frequency could enhance its efficacy and minimize any adverse effects, thus improving the overall management of VVA.

Spd, a polyamine found in all living cells, is endowed of an array of key biological roles [16] by the promotion of tissue biomechanical resistance and reduction of atrophy through the support of microtubule network and gap junction integrity [17]. These properties support cell renewal and tissue repair, leading to improved anatomical and functional integrity.

When combined with an anionic biopolymer such as HA, cationic Spd produces supramolecular complexes, thus deemed of enhanced potency [8]. Previous pilot studies on local therapy with HA-Spd in women with vulvodynia have shown efficacy in reducing pain and improving sexual function [9]. The proposed mechanisms of action for HA, Spd-HA, and E2 is resumed in Figure 6.

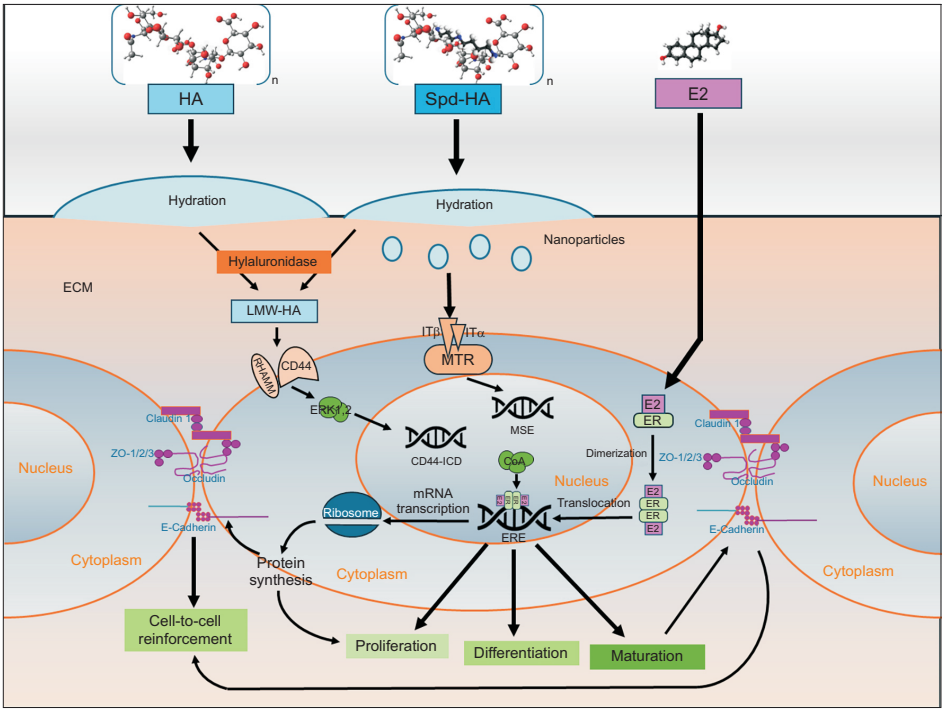

Fig. 6. Proposed mechanisms of action for the studied molecules: hyaluronic acid (HA), spermidine hyaluronate (Spd-HA) complex, and topical 17β-estradiol (E2). The figure illustrates the potential mechanisms of action on vaginal epithelial of E2, HA, and Spd-HA within the mucosa, extracellular matrix (ECM), and nucleus to enhance hydration and reinforce cell-to-cell interaction. Thicker arrows highlight established pathways and their primary mode of action, while thinner arrows indicate proposed secondary pathways. Topical E2, uses as drug, are lipophilic and they can diffuse across the cellular membranes. They interact with estrogen receptors (ERs), leading to receptor dimerization, nuclear translocation, and binding to estrogen receptor elements (ERE). This interaction activates coactivators (CoA), regulates gene transcription, and promotes protein synthesis, resulting in cellular proliferation and differentiation. HA and Spd-HA, classified as medical devices, primarily contribute to mucosal hydration. However, despite being the most well-known of these medical devices, HA also participates in intracellular signalling cascades. HA interacts with hyaluronan receptor (CD44) and hyaluronan-mediated motility receptor (RHAMM) receptors, influencing extra-cellular signal regulated kinase (ERK) 1/2 signalling and promoting mRNA transcription and protein synthesis, which subsequently stimulate cellular proliferation and differentiation. The Spd-HA complex similarly promotes intracellular pathways, interacting with CD44, leading to the activation of intracellular domains (CD44-ICD) and further influencing cellular signalling mechanisms that promote mucosal hydration and structural integrity. Additionally enhances mucosal hydration and maturation through various mechanosensing and mechanotransduction elements and interactions with integrins (ITα, ITβ). This is facilitated by nanoparticle formation, reinforcing the structural integrity and functionality of the mucosal barrier. LMW-HA: low molecular weight-HA, IT: integrins, MTR: mechanotransducers, MSE: mechanosensing elements, ZO: zona occludens.

This animal study suggest that Spd-HA gel, Ubigel Donna™, holds promise as a therapy for postmenopausal VVA, demonstrating improvements in various parameters of genital wellbeing. VVA significantly impacts women's physical, psychological, and sexual health [18]. Despite its prevalence after menopause, VVA is often accepted by women as an inevitable consequence of aging. Treatment options for VVA range from vaginal lubricants to hormonal topical applications. Hormonal therapy has been extensively studied and proven effective for this condition. However, many women are hesitant to use hormonal treatments due to concerns or contraindications such as hormone-dependent tumors, androgenetic alopecia, or persistent genital arousal disorders. For these patients, Ubigel Donna™ offer a valuable alternative for managing genitourinary syndromes [19].

Our findings from the OVX rat model suggest that Spd-HA gel may be a valid non-pharmacologic treatment for VVA. This gel combines the beneficial properties of Spd and HA, both of which play crucial roles in reproductive health. The Spd-HA complex provides benefits that are not significantly inferior to those of estrogen treatments, potentially offering a safe and effective alternative for managing VVA symptoms in postmenopausal women. A limitation of our study is the relatively small sample size in the HA group, which does not allow for a comprehensive analysis of all

comparisons. This group was included primarily to establish a baseline for the minimal effects of non-pharmacological treatments. Nevertheless, the conclusions regarding the observed effects of the Spd-HA complex remain robust, particularly when compared to estrogen treatment. Given these promising preclinical results, further research is warranted to translate these findings to human clinical trials. Estrogen therapy effectively alleviates VVA symptoms by enhancing mucosal elasticity, lowering pH, and improving natural lubrication, it also carries risks, including an increased likelihood of cardiovascular events and certain cancers [20-22]. Thus, there is a clear need for treatments that can provide similar benefits without these risks. The potential of Ubigel Donna™ as a non-hormonal therapy for VVA will address an unmet need in the treatment of this widespread postmenopausal condition, offering a safe option for women who cannot, or may desire to avoid estrogens. Further clinical studies in humans are essential to confirm the efficacy and safety of Spd-HA gel, leading to a new standard of care in VVA.

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CONFLICT OF INTEREST

Carlo Angelo Ghisalberti is the CEO of Tixupharma Srl, the patent holder of the Ubigel technology. Caterina Tezze is employed by Tixupharma Srl.

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