

# Clinical Effect of *Hibiscus taiwanensis* Extract on Women with Genitourinary Syndrome of Menopause

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## ABSTRACT

**Objective:** The deficiency of estrogen becomes clinically more overt over time and correlated with amounts of genitourinary syndromes of menopause (GSM). Our study aimed at examining the clinical effect of *Hibiscus taiwanensis* compound extract (HERCET®-w gel) on women with GSM. **Subjects and Methods:** This study included 31 patients with GSM symptoms. The treatment administered to patients included in this study was the daily use of vaginal treatment of HERCET®-w gel. Before, 3 months, and 6 months after HERCET®-w gel treatment, each patient's baseline characteristic data were collected. **Results:** Our data showed that HERCET®-w gel could significantly improve some index or questionnaire in urinary symptoms including the Urogenital Distress Inventory 6, the Vaginal Health Index, or pH value. It also showed a significant increase in sexual function after 6 months treatment of HERCET®-w. **Conclusion:** HERCET®-w on the women with GSM after 6 months could significantly improve GSM. It also showed an obvious progress of patients' sexual function in the Female Sexual Function Index score in the 6-month follow-up.

**KEYWORDS:** Genitourinary syndromes, *Hibiscus taiwanensis*, urinary symptoms

## INTRODUCTION

Due to the obvious change of hormone during the menopause, all estrogen-sensitive tissues were affected.<sup>[1]</sup> The apparent alteration of estrogen may lead to deficiency of organs including reproductive tract, urinary tract, heart, blood vessels, bones, breasts, skin, hair, mucous membranes, pelvic muscles, and brain.<sup>[2]</sup> The deficiency of estrogen becomes clinically more overt over time and correlated with amounts of genitourinary syndromes of menopause (GSM). GSM is usually defined as a group of symptoms which were caused by hypoestrogenic changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra,

and bladder. These syndromes mostly occur between ages 48–52 years, and they affect almost 20% of premenopausal women and 70% of postmenopausal women.<sup>[3]</sup> In clinical, current treatment to GSM approved by the Food and Drug Administration contained vaginal moisturizers, lubricants, and hormones. Other options not approved for GSM have also shown favorable outcomes. Although estrogen treatment is considered

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the most effective therapeutic option, many women prefer to avoid it due to the safety risk.<sup>[4,5]</sup> The North American Menopause Society stated that endometrial safety has not been studied in long-term clinical studies, and there are insufficient data to confirm the safety of local estrogen in women with breast cancer. Therefore, a novel treatment for GSM is urgently needed.

*Hibiscus taiwanensis* is an indigenous species of *Malvaceae* from Taiwan. It was originally used in landscape due to its changes of color. In Traditional Chinese Medicine, we often use their stems and plates in the herbal formula to clear lung heat, reduce inflammation, pain relief, detumescence, and blood-cooling effects.<sup>[6,7]</sup> Some studies also reported that extract of *H. taiwanensis* contained various biological activities such as antibacterial effect, antiviral, antioxidant, and antityrosinase activity.<sup>[8]</sup> There are also reports that the extract of hibiscus can improve the utilization of glucose and sensitivity to centipede and reduce hyperglycemia in diabetic patients.<sup>[9-11]</sup> The main component of *H. taiwanensis* was reported to possess lignan, ferulamide, tocopherol, and motherwort. Lignan is called plant-based estrogen.<sup>[12]</sup> Lignan not only plays a role in regulating estrogen but also stimulates hormone secretion through activating the estrogen gland. Ferulamide is a ferulic acid derivative and has a good antioxidative stress activity in previous reports.<sup>[13]</sup> Besides, the anti-inflammatory, analgesic, and antivirus effect and wound healing activity through nerve growth factor (NGF) were also investigated.<sup>[14,15]</sup> NGF is a kind of nutrition that promotes the development of the nervous system, wound healing, and regulating mast cells. Due to the massive biological activity, it might be a potential agent toward GSM.

Our study intended to use *Hibiscus taiwanensis* compound extract (HERCET®-w gel) on patients with GSM to fully assess the therapeutic effect of HERCET®-w gel. We examined the effect of HERCET®-w gel on GSM with urinary-related questionnaires, serum estradiol, sexual function questionnaire, and life quality questionnaire to validate the beneficial effect of HERCET®-w gel on each aspect of GSM.

## SUBJECTS AND METHODS

### Subjects and experimental reagents

This study included 31 patients (mean age:  $61.7 \pm 6.7$  years) with GSM symptoms. The exclusion criteria included other causes with similar symptoms and, specifically, dermatological conditions of the vulva such as lichen sclerosus or planus, eczema, dermatitis, chronic vulvovaginitis, vaginitis and vaginosis,

vulvodynia, malignancies, and chronic pelvic pain. The HERCET®-w gel was provided by JARIO Health Herbal Care Corp (Taipei, Taiwan). The batch number of HERCET®-w gel was MFG20180511. The International Nomenclature of Cosmetic Ingredients (INCI) name is *H. taiwanensis* extract and the INCI monograph ID is 35818. The contents of HERCET®-w gel included water, HERCET® (*H. taiwanensis* extract), panthenol, carbomer, betaine, propanediol, trehalose, arginine, sodium hyaluronate, glyceryl polymethacrylate, propylene glycol, polyvinyl methyl ether/maleic acid copolymer, *Matricaria chamomilla*, and butylene glycols. The ingredients were also registered in the American Chemical Society as CAS No. 2906877-99-2. The whole plant was used to extract. The treatment administered to patients included in this study was the daily use of vaginal treatment of HERCET®-w gel. The smear area covered the entire vaginal wall and vulva. This movement was performed once a day and sustained for 6 months.

### Assessment of female stress urinary incontinence in subjects

Before, 3 months, and 6 months after HERCET®-w gel treatment, each patient's baseline characteristic data were collected. A personal interview was conducted in the following battery of questionnaires: the Urogenital Distress Inventory 6 (UDI-6), the Incontinence Impact Questionnaire 7 (IIQ-7),<sup>[16]</sup> the Overactive Bladder Symptom Score (OABSS),<sup>[17]</sup> and the Vaginal Health Index (VHI)<sup>[18]</sup> to assess the effect of HERCET®-w gel on GSM urinary symptoms and collected serum from patients for measuring follicle-stimulating hormone (FSH) and estradiol (E2). The pH value was also tested before, 3 months, and 6 months after HERCET®-w gel treatment.

### Assessment of female sexual function index in subjects

The sexual function and vaginal health were acquired before, 3 months, and 6 months after HERCET®-w gel treatment through the following questionnaires: the Female Sexual Function Index (FSFI)<sup>[19]</sup> and the Vulvovaginal Symptoms Questionnaire (VSQ).<sup>[20]</sup> All incontinence patients and the control group were asked to fill out the FSFI questionnaire form in the outpatient department. The FSFI is a reliable and validated measure of women's sexual function. It has 19 questions that assess six areas of sexual function, including desire, arousal, lubrication, orgasm, satisfaction, and pain. The score range for items 3–14 and 1–19 is from 0 to 5, and for items 1, 2, 15, and 16 is from 1 to 5.<sup>[12]</sup> The composite score is determined by the sum of the domains multiplied by a factor domain point. The full

range of scores is from 2 to 36, with higher scores indicating lower levels of sexual dysfunction.

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The data were reported as means  $\pm$  SD. The IBM SPSS statistic 20 (IBM, NY, USA), paired sample *t*-test, or Chi-square test was used for comparison between the two groups. Differences were considered statistically significant at  $P < 0.05$ .

## RESULTS

### Participants and basic characteristic description

Thirty-one patients were recruited in this study. The mean age of these patients was  $61.7 \pm 6.7$  years. We followed up their status till 6 months after vaginal treatment of HERCET®-w gel [Table 1].

### Effect of HERCET®-w gel treatment in genitourinary syndromes of menopause patients on serum index, pH, and female stress urinary incontinence

We first examined the effect of vaginal treatment of HERCET®-w gel on GSM patients in urinary symptoms

and acquired the questionnaires at baseline, 3 months after treatment, and 6 months after treatment. The result showed that the UDI-6 score significantly improved from  $22.4 \pm 16.2$  to  $16.8 \pm 12.9$  in the 3-month follow-up data ( $P = 0.016$ ). However, treatment of HERCET®-w in UDI-6 on 6-month follow-up changed from  $22.4 \pm 16.2$  to  $17.6 \pm 11.4$  ( $P = 0.08$ ), and it did not show an obvious effect on urogenital distress in 6-month follow-up. In the IIQ-7 questionnaire, treatment of HERCET®-w changed the score from  $11.1 \pm 16.2$  to  $9.2 \pm 14.3$  and  $11.1 \pm 16.2$  to  $8.1 \pm 12.2$  in 3-month and 6-month follow-up ( $P = 0.33$  and  $P = 0.38$ ), respectively. It showed a decline trend but did not reveal a significant difference. Then, OABSS scores were also validated. Vaginal treatment of HERCET®-w in OABSS changed from  $4.3 \pm 2.2$  to  $4.2 \pm 2.4$  ( $P = 0.82$ ) in the 3-month follow-up and from  $4.3 \pm 2.2$  to  $3.8 \pm 1.9$  ( $P = 0.24$ ) in the 6-month follow-up. Then, the treatment of HERCET®-w on VHI score was revealed. The data showed that the VHI score changed from  $10.1 \pm 2.5$  to  $15.2 \pm 3.2$  ( $P = 0.001$ ) in 3-month follow-up and  $10.1 \pm 2.5$  to  $16.0 \pm 3.8$  ( $P = 0.001$ ) in the 6-month follow-up. Besides, the FSH score after HERCET®-w treatment changed from  $52.7 \pm 20.0$  to  $50.8 \pm 20.3$  ( $P = 0.39$ ) in the 3-month follow-up and from  $52.7 \pm 20.0$  to  $51.3 \pm 20.8$  ( $P = 0.34$ ) in the 6-month follow-up. The data showed no significant difference. We also tested serum levels of E2 from patients. The results showed no significant difference in the 3-month follow-up and 6-month follow-up. The pH value was also examined. Our data showed that vaginal treatment of HERCET®-w significant downregulated pH value from  $6.7 \pm 1.0$  to  $6.11 \pm 0.8$  ( $P = 0.005$ ) in 3-month follow-up and from  $6.7 \pm 1.0$  to  $5.8 \pm 0.9$  ( $P = 0.001$ ) in 6-month follow-up [Table 2].

### Effect of HERCET®-w gel treatment in genitourinary syndromes of menopause patients on female sexual function indexes

We then acquired sexual function under HERCET®-w gel treatment. Our data showed that the FSFI total score

**Table 1: Demographic data of enrolled patients**

Mean age (years)	61.7 $\pm$ 6.7
Follow-up (months)	6

Values are expressed as mean $\pm$ SD or *n*. SD: Standard deviation

**Table 2: Urinary-related questionnaire results at baseline and 3 and 6 months posttreatment of *Hibiscus taiwanensis* compound extract**

	Baseline	3 months posttreatment	6 months posttreatment	<i>P</i>	
				3 months	6 months
UDI-6	22.4 $\pm$ 16.2	16.8 $\pm$ 12.9	17.6 $\pm$ 11.4	0.016*	0.080
IIQ-7	11.1 $\pm$ 16.2	9.2 $\pm$ 14.3	8.1 $\pm$ 12.2	0.33	0.38
OABSS	4.3 $\pm$ 2.2	4.2 $\pm$ 2.4	3.8 $\pm$ 1.9	0.82	0.24
VHI	10.1 $\pm$ 2.5	15.2 $\pm$ 3.2	16.0 $\pm$ 3.8	0.001*	0.001*
FSH	52.7 $\pm$ 20.0	50.8 $\pm$ 20.3	51.3 $\pm$ 20.8	0.39	0.34
E2	12.5 $\pm$ 3.6	13.6 $\pm$ 5.0	13.1 $\pm$ 4.6	0.45	0.52
pH	6.7 $\pm$ 1.0	6.11 $\pm$ 0.8	5.8 $\pm$ 0.9	0.005*	0.001*

\*Statistical significance, paired *t*-test. Values are expressed as mean $\pm$ SD or *n*. UDI-6: Urogenital Distress Inventory 6, IIQ-7: Incontinence Impact Questionnaire 7, OABSS: Overactive Bladder Symptom Score, VHI: Vaginal Health Index, FSH: Follicle-stimulating hormone, E2: Estradiol, SD: Standard deviation

slightly elevated from  $8.9 \pm 7.4$  to  $11.9 \pm 10.1$  ( $P = 0.13$ ) in the 3-month follow-up and significantly increased from  $8.9 \pm 7.4$  to  $13.2 \pm 9.8$  ( $P = 0.007$ ). In the desire and arousal domain, treatment of HERCET®-w did not affect both domains in 3 months or 6 months. However, HERCET®-w gel significantly increased in the rest of four domains in the 6-month follow-up. It elevated lubrication from  $1.4 \pm 1.4$  to  $2.2 \pm 1.9$  ( $P = 0.011$ ), orgasm from  $1.5 \pm 1.6$  to  $2.2 \pm 1.8$  ( $P = 0.017$ ), satisfaction from  $1.7 \pm 1.9$  to  $2.5 \pm 2.0$  ( $P = 0.021$ ), and pain from  $1.3 \pm 1.4$  to  $2.4 \pm 2.2$  ( $P = 0.007$ ). Besides, 71% (22 in 31 cases) felt the efficacy of HERCET®-w in 3-month follow-up and 64.5% (20 in 31 cases) in 6-month follow-up [Table 3].

### Effect of HERCET®-w gel treatment in genitourinary syndromes of menopause patients on quality of life indexes

We finally examined the VSQ score to assess the patient's quality of life. Our data showed that HERCET®-w showed a significant improvement in every index in the VSQ questionnaire not only in 3-month follow-up but also in 6-month follow-up. In the data after 3 months treatment, HERCET®-w gel changed itchy from  $2.2 \pm 2.4$  to  $0.8 \pm 1.4$  ( $P = 0.001$ ), tenderness from  $3.7 \pm 3.4$  to  $1.1 \pm 1.9$  ( $P = 0.001$ ), irritation from  $4.3 \pm 3.2$  to  $0.8 \pm 1.4$  ( $P = 0.001$ ), burning from  $2.3 \pm 2.6$

to  $0.8 \pm 1.5$  ( $P = 0.001$ ), discharge from  $1.5 \pm 2.5$  to  $0.6 \pm 1.3$  ( $P = 0.017$ ), and discomfort from  $5.8 \pm 2.6$  to  $1.5 \pm 1.7$  ( $P = 0.001$ ). The 6-month follow-up also showed a similar trend as 3-month data [Table 4].

## DISCUSSION

Our current study aimed at investigating the clinical therapeutic effect of HERCET®-w gel on GSM patients in urinary symptoms, sexual function, and daily life quality. Our data showed that HERCET®-w gel could significantly improve some index or questionnaire in urinary symptoms including UDI-6, VHI, or pH value. It also showed a significant increase of sexual function after 6 months treatment of HERCET®-w. To our excitement, we observed the comprehensive elevation of patients' quality of life through the VSQ questionnaire. HERCET®-w is one kind of plant extract obtained from *H. taiwanensis*. As a matter of fact, some research also intended to use the extract of natural products or herbal medicine handling with GSM or other disorders.

Many researchers obtained natural products from the herbal plants or marine organisms which possess various bioactivities. Some of them were used on treating disorders of the urinary systems such as *Serenoa repens*. Morgia et al. 2013 showed that *S. repens* which was derived from the berries of the saw palmetto tree could

**Table 3: Changes of female sexual function index scores at baseline and 3 and 6 months posttreatment of *Hibiscus taiwanensis* compound extract**

	Baseline	3 months posttreatment	6 months posttreatment	P	
				3 months	6 months
FSFI	8.9±7.4	11.9±10.1	13.2±9.8	0.130	0.007*
Desire	1.7±0.8	2.1±1.3	2.1±1.0	0.127	0.054
Arousal	1.4±1.3	1.7±1.6	1.8±1.5	0.258	0.074
Lubrication	1.4±1.4	2.0±2.0	2.2±1.9	0.130	0.011*
Orgasm	1.5±1.6	1.9±1.9	2.2±1.8	0.247	0.017*
Satisfaction	1.7±1.9	2.2±2.1	2.5±2.0	0.270	0.021*
Pain	1.3±1.4	2.1±2.0	2.4±2.2	0.051	0.007*
Efficacy (%)				22/31 (71.0)	20/31 (64.5)

\*Statistical significance, paired *t*-test. Values are expressed as mean±SD or *n*. SD: Standard deviation, FSFI: Female Sexual Function Index

**Table 4: Vulvovaginal Symptoms Questionnaire results at baseline and 3 and 6 months posttreatment of *Hibiscus taiwanensis* compound extract**

	Baseline	3 months posttreatment	6 months posttreatment	P	
				3 months	6 months
Itchy	2.2±2.4	0.8±1.4	0.8±1.7	0.001*	0.011*
Tenderness	3.7±3.4	1.1±1.9	1.0±2.0	0.001*	0.001*
Irritation	4.3±3.2	0.8±1.4	0.9±1.9	0.001*	0.001*
Burning	2.3±2.6	0.8±1.5	0.7±1.6	0.001*	0.002*
Discharge	1.5±2.5	0.6±1.3	0.3±0.8	0.017*	0.010*
Discomfort	5.8±2.6	1.5±1.7	1.8±2.3	0.001*	0.001*
Efficacy				29/31 (93.6%)	27/31 (87.1%)

\*Statistical significance, paired *t*-test. Values are expressed as mean±SD or *n*. SD: Standard deviation



obviously ameliorate the inflammation and stage of benign prostatic hyperplasia (BPH). The mechanism of action of *S. repens* worked through reducing the level of CD20, CD3, CD68, and PSA value. They showed that the combination of *S. repens*, lycopene, and selenium might have the best anti-inflammatory activity on treating BPH patients.<sup>[21]</sup> Because of the very low concentrations of therapeutic compounds in plants, their exhaustive recovery becomes a crucial issue to obtain high yields of the products with the use of an extractive method that should be reproducible.

Chen *et al.* 2014 also screened potential herbal medicines against stress urinary incontinence (SUI) through an *ex vivo* organ bath assay. *Ramulus Cinnamomi* and its major constituent cinnamaldehyde cause a high contractile force of the urethra and a low contractile force of blood vessels. Cinnamaldehyde significantly inhibited lipopolysaccharide-induced nitric oxide (NO) production and inducible NO synthase expression in RAW264.7 cells. Besides, cinnamaldehyde significantly reversed the vaginal distension-induced SUI physical signs and reduced blood pressure in SUI mice model.<sup>[22]</sup> Li *et al.* 2016 presented a 35-year-old case who developed SUI following forceps delivery and was treated successfully with appropriate acupuncture and Chinese herbs.<sup>[23]</sup> However, most research did not apply it on the clinical case or recorded the data with a quantifiable questionnaire. Our research not only applied HERCET®-w gel on multiple clinical cases but also measured the data with various quantifiable questionnaires. The result showed that UDI-6 and VHI score significantly improved in the 3-month follow-up data. The pH value also significantly downregulated in the 3-month follow-up. Besides, obvious impacts on VHI score and pH value were still evident in the 6-month follow-up data. Except for the impact on the urinary system, some research also used herbal extracts on improving sexual function.

Dongre *et al.* 2015 showed that a high-concentration Ashwagandha root extract (HCARE) supplementation was used for improving sexual function in healthy females. Fifty individuals were recruited in their study and consumed either HCARE or placebo capsules of 300 mg twice daily for 8 weeks. The results showed that FSFI score significantly improved in FSFI total score from 13.63 to 23.86, and almost every index showed an apparent increase except for desire and pain. They also examine the Female Sexual Distress Scale score and it also significantly ameliorated through the treatment of HCARE supplementation.<sup>[24]</sup> Bosak *et al.* 2022 used chamomile, which is commonly used in many human ailments such as hay fever, inflammation,

muscle spasms, menstrual disorders, insomnia, ulcers, and wounds. They investigated the effectiveness of chamomile vaginal gel in comparison with that of placebo vaginal gel and conjugated estrogen vaginal cream as a standard treatment on the sexual function of postmenopausal women. Their results depicted that vaginal treatment of chamomile vaginal gel for 3 months could significantly improve sexual function in GSM patients. The findings showed that chamomile vaginal gel in comparison to placebo vaginal gel caused a significant improvement in all six sexual function domains, and the total FSFI score increased from  $16.7 \pm 1$  to  $28.8 \pm 0.36$ . They also emphasized this gel could be considered as a treatment option for postmenopausal women with sexual dysfunction, especially in those for whom using synthetic estrogen was contraindicated. Although some side effects were observed in the use of chamomile vaginal gel,<sup>[25]</sup> our study also showed an obvious amelioration of sexual function in the vaginal treatment of HERCET®-w for 6 months but not in 3-month follow-up. The recovery showed in every index of the FSFI questionnaire including desire, arousal, lubrication, orgasm, satisfaction, pain, and total score.

Some studies focused on the vaginal condition in GSM patients. Yaralizadeh *et al.* 2016 demonstrated that extract of fennel got positive effects on vaginal atrophy symptoms including dryness, pallor, itching, and dyspareunia in postmenopausal women, which may be due to the presence of a biologically active compound called phytoestrogen. In this study, the vaginal cream form had been used for research, but postmenopausal women were followed up for only 8 weeks.<sup>[26]</sup> Besides, the effect of licorice vaginal cream was shown in the study by Sadeghi *et al.* 2020. The results showed that licorice vaginal cream significantly improved the mental symptoms of vaginal atrophy (itching, burning, dyspareunia, and dryness) compared to placebo also in 8-week follow-up.<sup>[27]</sup> The effects of chamomile gel, mentioned above, also examined the VSQ score. Their results showed that chamomile vaginal gel cream and conjugated estrogen vaginal cream both significantly ameliorated mental symptoms of vaginal atrophy (burning, itching, intercourse pain, and vaginal dryness) compared to placebo in 12-week follow-up.<sup>[25]</sup> By contrast, our study showed both 12-week and 24-week follow-ups, and the data showed that HERCET®-w showed a significant improvement in every index in the VSQ score not only in 3-month follow-up but also in 6-month follow-up.

To sum up our study, we showed that vaginal treatment of HERCET®-w on the women with GSM after 6 months

could significantly improve some indexes in urinary symptoms including UDI-6, VHI, and pH value. It also showed an obvious progress of patients' sexual function with FSFI score in 6-month follow-up. Furthermore, vaginal treatment of HERCET®-w also significantly reversed GSM-induced vaginal atrophy symptoms. It showed a significant improvement in 3-month and 6-month follow-up. However, more randomized trials and longer follow-ups should be performed to evaluate the safety and durability of this new treatment to benefit women suffering from GSM.

## CONCLUSIONS

The vaginal treatment of HERCET®-w on the women with GSM after 6 months could significantly improve UDI-6, VHI, and pH values which represent the urinary conditions. It also showed an obvious progress of patients' sexual function with FSFI score in 6-month follow-up. Furthermore, vaginal treatment of HERCET®-w also significantly reversed GSM-induced vaginal atrophy symptoms.

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## Conflicts of interest

There are no conflicts of interest.

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