

## Article

# Clinical Experience with a Medical Device Containing Xyloglucan, Hibiscus, and Propolis for the Control of Acute Uncomplicated Urinary Tract Infection-like Symptoms

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**Abstract:** Background: The development of drug resistance among causative agents has resulted in the need to change the paradigm toward alternative therapeutic approaches for uncomplicated urinary tract infections (UTIs). The objective of the present study was to evaluate the efficacy of an oral medical device containing xyloglucan, hibiscus, and propolis in clinical practice with a cohort of women from Switzerland with UTI-like symptoms and the administration of concomitant drugs. Materials and Methods: This work describes an observational, prospective, and multicenter study involving 103 women attending a primary care physician for a symptomatic episode, or recurrence, of acute uncomplicated cystitis between August 2018 and June 2019. Utipro<sup>®</sup>Plus was administered orally, with patients being prescribed two capsules per day for 5 days to control discomfort symptoms or one capsule per day for 15 consecutive days per month (followed by a 15-day break for a 3-month cycle) to prevent recurrences. Results: A total of 84 women (81.6%) did not require an additional consultation, whereas 17 (16.5%) required a second one. Inadequate treatment response was found in 7 women out of the 19 who required a further consultation (36.8%): 3 women with no history of cystitis (out of 13, 23.1%) and 4 with recurrent cystitis (out of 6, 66.7%). None of the women from the study reported an adverse event. Conclusions: The studied product containing xyloglucan, hibiscus, and propolis is safe and effective for the treatment of a broad spectrum of women with acute uncomplicated or recurrent UTI-like symptoms.

**Keywords:** medical device; xyloglucan; urinary tract infection; clinical; experience

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## 1. Introduction

Urinary tract infections (UTIs) are one of the most prevalent urologic diseases [1], affecting 50–60% of adult women in their lifetime [2]. With the COVID-19 pandemic and SARS-CoV-2 management, there was a reduction in attention to bacterial infections [3]. However, more than 60% of patients are hospitalized with COVID-19 and urinary tract co-infections [4,5]. Uropathogenic *Escherichia coli* is responsible for about 80% of cases and is associated with a risk of recurrence. Indeed, more than 30% of women experience another infection within 12 months after symptom resolution [6]. In turn, the recurrence is positively correlated with anxiety, depression, and impaired quality of life [7]. UTIs are classified depending on the presence of relevant functional/anatomical complications. Acute uncomplicated cystitis is thus a lower urinary tract infection (LUTI), with severe symptoms such as urinary urgency or dysuria [1]. Infections occurring in the upper urinary tract are known as pyelonephritis; infections are considered known as cystitis if they are located in the lower urinary tract [8]. Risk factors associated with cystitis include female gender, age, history of UTI, sexual activity, and comorbidities [9]. Antimicrobials are the first-line therapy for uncomplicated UTIs [9], aiming to alleviate symptoms and reduce recurrence. Nevertheless, the development of drug resistance is changing the paradigm toward alternative therapeutic approaches [10]. European guidelines recommend counselling, behavioral

modifications, and non-antimicrobial measures to prevent recurrence [11]. In 2016, a novel class III medical device (Utipro<sup>®</sup>Plus; Noventure, Barcelona, Spain) containing xyloglucan, *Hibiscus sabdariffa*, and propolis was approved in the European Union for the control and prophylaxis of UTIs [12]. Xyloglucan is a hemicellulose that creates a protective barrier that is able to prevent the adherence and invasion of uropathogens in the bowel lumen [13] while also acidifying the urine pH to avoid bacterial growth [14]. The efficacy and safety of this product have been evidenced via in vitro studies [15,16], rodents [17,18], and humans [9–22]. Moreover, this product is considered to be an alternative approach to conventional treatments for recurrent urinary tract infections by the Swiss Society of Gynecology and Obstetrics [23]. The objective of the present study was to evaluate the efficacy of this therapeutic approach in clinical practice with a cohort of women from Switzerland, paying special attention to the recurrence of UTIs, UTI-like symptoms and the administration of concomitant drugs. Based on previous works, in our study, which included a larger group of patients, we hypothesized a significant improvement in UTI-like symptoms after treatment with Utipro<sup>®</sup>Plus.

## 2. Materials and Methods

### 2.1. Study Design

An observational, prospective, multicenter study involving women from Switzerland attending a primary care physician for a symptomatic episode or recurrence of acute uncomplicated cystitis was performed between August 2018 and June 2019. A UTI-like symptom was considered recurrent when the patient had  $\geq 2$  symptomatic episodes in the last 6 months or  $\geq 3$  symptomatic episodes in 12 months. All women signed informed consent to participate in the study. The decision to enroll a woman was based on the physician's decision to treat her with the product (Utipro<sup>®</sup>Plus). The study consisted of a single consultation (and recruitment) visit. If the patient required an additional consultation within 7 days of the initial visit, information from that visit was also included in the study. Performed in Switzerland, this is an observation and a post-commercialization study that used anonymized health-related personal data that do not come under the scope of the Human Research Act (HRA) and are therefore not subject to ethical approval from an Ethics Committee, according to the Coordination Office for Human Research and as stated by the Ethics Committee of the participating Hospitals. This study was completed in accordance with the Declaration of Helsinki as revised in 2013.

### 2.2. Medical Device Characteristics and Doses

All women received treatment with Utipro<sup>®</sup>Plus according to the manufacturer's instructions [10]. Utipro<sup>®</sup>Plus is a class III medical device complying with European Union (EU) Medical Devices Directive 93/42/EEC and its subsequent amendments (CE 0373, Noventure SL). Utipro<sup>®</sup>Plus contains xyloglucan 100 mg, gelatin 50 mg, propolis 100 mg, and *Hibiscus sabdariffa* 100 mg; it also contains silicon dioxide, magnesium stearate, and corn starch. It is administered orally, with the following recommended administration: 2 capsules per day (1 every 12 h) for 5 days to control discomfort symptoms or 1 capsule per day for at least consecutive days per month followed by a 15-day break for a 3-month cycle to prevent a recurrence. In some cases, the doses and the time of treatment were modified by the clinician's decision.

### 2.3. Data Collection and Variables

During or after consultations, physicians completed an online structured questionnaire containing information on symptomatology: onset of symptoms, the urinary frequency with small amounts, dysuria, urinary urgency, urinary retention, suprapubic pain, hematuria, and fever. Additionally, physicians collected the available demographic and clinical data of the women from their medical charts. Quantitative data were expressed as median and range (minimum–maximum values), whereas qualitative data were expressed as absolute and relative frequencies (%).

### 3. Results

#### 3.1. Study Population

A total of 21 primary care physicians recruited 103 women for the study. Women had a median age of 47 years (range 19–87 years; Table 1). In total, 68 women (66.0%) attended the specialist due to a first symptomatic episode of acute uncomplicated cystitis, whereas 35 (34.0%) had recurrent cystitis. Hypertension (30.8%) and type 2 diabetes (23.1%) were the most frequent comorbidities. Considering factors potentially associated with UTIs 75 women (72.3%) showed at least one of them: post-menopausal/climacteric syndrome (32 women, 42.7% of those with factors), frequent sexual activity (18 women, 24.0%), premenstrual problems (6 women, 8.0%), diabetes (5 women, 6.7%), or others (12 women, 16%; irritable bowel syndrome, vaginal dryness, obesity).

A total of 63 women (out of 100 with available information, 63.0%) had nitrites in their urine. Moreover, according to the laboratory results, 83.3% of the patients tested were leukocyte-esterase positive. *E. coli* was the most frequent microbiological agent (in 11 women out of 24 with positive findings, 25.6%).

Symptoms of current episodes of acute uncomplicated cystitis were predominantly initiated 3 days before consultation (55 women, 53.4%). The characteristics of episodes with UTI-like symptoms are shown in Table 2. Most women showed urinary frequency (7–8 times a day in 37 women, 35.9%; 9–10 times a day in 40, 38.8%). Urinary urgency that was considered moderate or strong was reported by 35 (34.0%) and 41 women (39.8%), respectively. Suprapubic pain was predominantly indicated as moderate (28 women, 27.2%) and strong (37 women, 35.9%). Hematuria (strong) was reported by 75 women (72.8%).

#### 3.2. Therapeutic Management

The median duration of the treatment with the medical device was 5 days (range 3–15 days) (Table 3). In women receiving treatment for secondary prevention (prophylaxis), the median duration of the treatment was 15 days (range 2–50 days).

The therapeutic management for the current episode of acute uncomplicated cystitis is shown in Table 3.

In total, 46 women (44.7%) received concomitant medication for the episode: 27 (26.2%) with no history of cystitis and 19 (18.4%) with recurrent cystitis (Figure 1). Antibiotics (23 women, 50.0% of those receiving a concomitant treatment) and nonsteroidal anti-inflammatory drugs (14 women, 30.4%) were the most frequently prescribed medications (Table 3). A total of 84 women (81.6%) did not require an additional consultation, whereas 19 required a second or a third one (17 and 2 required a second or a third consultation, respectively) (Figure 1). The median number of days from the first to the second consultation was 7 days (range 2–56 days). Inadequate response to the treatment was found in 7 women out of the 19 who required a further consultation (36.8%): 3 with no history of cystitis and 4 with recurrent cystitis. Only two women required a third, and last, follow-up consultation (both with recurrent cystitis). None of the women from the study reported an adverse event.

**Table 1.** Sociodemographic and clinical characteristics of women.

	<b>Total Women (N = 103)</b>
<b>Age, median years (range)</b>	47 (19–87)
<b>Diagnosis of cystitis, n (%)</b>	
First episode	68 (66.0)
Recurrent	35 (34.0)
<b>Number of recurrent episodes, median (range)</b>	
In the last 6 months	3 (0–5)
In the last 12 months	5 (1–10)
<b>Time since the last episode, median days (range)</b>	44.5 (12–416)
<b>Comorbidities, n (%)</b>	13 (12.6)
Hypertension	4 (30.8)
Type 2 diabetes	3 (23.1)
Cystocele	1 (7.7)
Rectocele	1 (7.7)
Abdominal complaints	1 (7.7)
Depression	1 (7.7)
Dementia	1 (7.7)
Others	1 (7.7)
<b>Factors potentially associated with UTI-like symptoms, n (%)</b>	75 (72.3)
Post-menopausal/climacteric syndrome	32 (42.7)
Frequent sexual activity	18 (24.0)
Premenstrual problems	6 (8.0)
Diabetes	5 (6.7)
Others	12 (16)
Not specified	4 (33.4)
Irritable bowel syndrome	2 (16.8)
Vaginal dryness	1 (8.3)
Obesity	1 (8.3)
<b>Laboratory results, n (%)</b>	
Nitrites in urine, n available	100
Positive	63 (63.0)
Leukocyte-esterase in urine, n available	90
Positive	75 (83.3)
Microbiological findings in urine culture, n available	43
Positive	24 (55.8)
<i>Escherichia coli</i>	11 (25.6)
<i>Klebsiella pneumoniae</i>	4 (9.3)
<i>Staphylococci</i> spp.	1 (2.3)
Mixed culture	1 (2.3)
Not specified, $\geq 10,000$ CFU	4 (9.3)
Not specified, $\geq 1000$ CFU	3 (7.0)

UTI, urinary tract infection; CFU, colony-forming units.

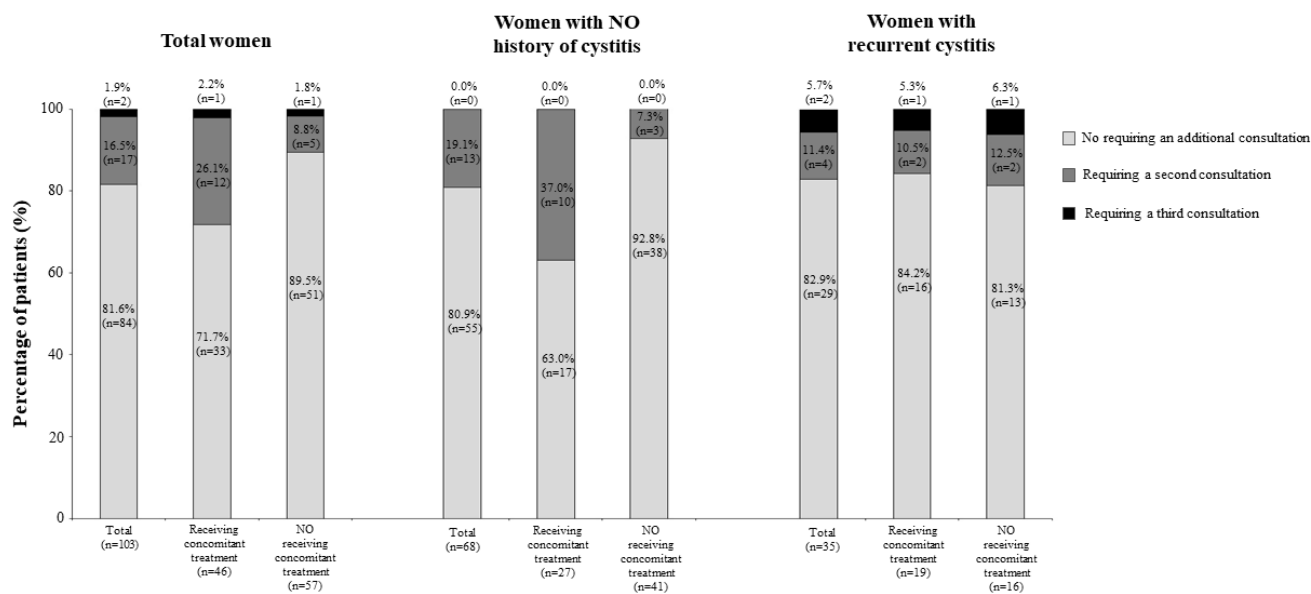
**Table 2.** Characteristics of episodes with acute uncomplicated cystitis-like symptoms.

	<b>Total Women (N = 103)</b>
The onset of symptoms, days before consultation (%)	
≥3 days	55 (53.4)
2 days	29 (28.2)
1 day	19 (18.4)
Fever (body temperature ≥ 37 °C)	2 (1.9)
Urinary frequency, small amounts; n (%)	
No frequent (up to 4 times a day)	6 (5.8)
Somewhat more frequent than usual (5–6 times a day)	20 (19.4)
Noticeably more frequent (7–8 times a day)	37 (35.9)
Very frequent (9–10 times a day)	40 (38.8)
Strong, involuntary urge to urinate, n (%)	
No	11 (10.7)
Yes, a little	16 (15.5)
Yes, moderate	35 (34.0)
Yes, strong	41 (39.8)
Pain and burning when urinating	
No	9 (8.7)
Yes, a little	20 (19.4)
Yes, moderate	35 (34.0)
Yes, strong	39 (37.9)
Feeling of not emptying the bladder fully	
No	8 (7.8)
Yes, a little	25 (24.3)
Yes, moderate	31 (30.1)
Yes, strong	39 (37.9)
Suprapubic pain, n (%)	
No	11 (10.7)
Yes, a little	27 (26.2)
Yes, moderate	28 (27.2)
Yes, strong	37 (35.9)
Blood in the urine (reddish color the urine)	
No	1 (1.0)
Yes, a little	4 (3.9)
Yes, moderate	23 (22.3)
Yes, strong	75 (72.8)

**Table 3.** Therapeutic management of the episode of acute uncomplicated cystitis.

	Total (N = 103)	Women with NO History of Cystitis (N = 68)	Women with Recurrent Cystitis (N = 35)
<b>Medical device</b>			
Median capsules per day (range)	2 (2–3)	2 (2–3)	2 (2–3)
Duration of treatment, median days (range)	5 (3–15)	5 (3–15)	5 (5–15)
<b>Receiving concomitant medication, n (%)</b>			
Antibiotics	23 (50.0)	11 (40.7)	12 (63.2)
NSAIDs	14 (30.4)	11 (40.7)	3 (15.8)
Lactobacilli/estrogen (Gynoflor®)	7 (15.2)	5 (18.5)	2 (10.5)
Antiseptic	6 (13.0)	5 (18.5)	1 (5.3)
Parasympatholytics	3 (6.5)	3 (11.1)	0 (0.0)
Spasmolytics	2 (4.3)	1 (3.7)	1 (5.3)
Antifungal	1 (2.2)	1 (3.7)	0 (0.0)
Beta-3 adrenoceptor agonist	1 (2.2)	1 (3.7)	0 (0.0)
Other	1 (2.2)	0 (0.0)	1 (5.3)
Virostatic	1 (2.2)	1 (3.7)	0 (0.0)
Sugar (D Mannose)	1 (2.2)	1 (3.7)	0 (0.0)
Homeopathy	1 (2.2)	1 (3.7)	1 (5.3)

NSAID, nonsteroidal anti-inflammatory drugs.



**Figure 1.** Women requiring additional consultations for the management of cystitis.

**4. Discussion**

UTIs are a worldwide health issue that imposes a significant burden on the economy, healthcare resources, and individuals [1,2]. After an initial UTI, approximately 20–30% of women with a UTI will have a second UTI within 6 months [24]. Moreover, 61.9% of patients suffering from recurrent UTI exhibited some degree of depression at baseline (day 0) and it was observed in several studies that recurrent UTIs have a significant impact on quality of life in women [25,26].

Antimicrobials have demonstrated efficacy for the control and prevention of acute uncomplicated UTIs [9]; however, the increase in antimicrobial resistance is stimulating the use of alternative approaches. In this line, Beerepoot et al. [27], in a systematic review and meta-analysis on nonantibiotic prophylaxis for recurrent UTIs, showed that the oral immunostimulant OM-89, cranberries, and acupuncture reduce the rate of UTI recurrence. Darouiche et al. [28], in a multicenter randomized controlled trial, revealed that the probiotic *E. coli* HU2117 reduces the frequency of infection in women with recurrent UTIs. Similarly, Wagenlehner et al. [29], in a double-blind, randomized, and multicenter, phase III study, revealed that herbal therapy with the product BNO 1045 was non-inferior to antibiotic therapy with fosfomycin for women with newly diagnosed acute uncomplicated UTI.

On the other hand, cystitis is primarily caused by mucosal infection of the bladder by intestinal bacteria. Based on this, the novel product under evaluation, which contains xyloglucan, hibiscus, and propolis, minimizes the adhesion and proliferation of uropathogens in the intestinal lumen and avoids their migration from the urethra to the bladder [12]. Diverse studies have confirmed the efficacy and safety of this oral medical device for acute uncomplicated UTIs [15–22]. Costache et al. [22] carried out a multicenter, double-blind, randomized phase IV clinical trial involving 40 women with a symptomatic episode of uncomplicated UTI who received the medical device or placebo as adjuvant therapy to antimicrobials. The authors showed that after 5 days of treatment, the number of patients with positive culture decreased from 20 to 1, irrespective of the treatment. By day 11, culture positivity (mainly by *E. coli*) was found in 0% and 45% of patients receiving the medical device or placebo, respectively. By day 76, UTI recurrence occurred in 15% and 70% of patients, receiving the medical device or placebo, respectively. Furthermore, patients receiving the medical device showed a significant reduction in the frequency of urinary incontinence and urgency of micturition compared to the patients who received the placebo. No adverse events related to the studied product were reported. Moreover, Salvatorelli N et al. [20] also showed that after 6 months, symptomatic recurrence among patients treated with this medical device was reduced by 19.4% compared with the placebo group ( $p = 0.015$ ). In the García-Larrosa and Alexe study, only 3 of 30 patients (10%) in the group using the medical device required antibiotic treatment in comparison to 10 of 30 (33.3%) of the patients in the placebo group ( $p = 0.028$ ) [19]. In a systematic review and meta-analysis, Cai et al. [30] compared the effectiveness and safety profile of the same medical device (containing xyloglucan, hibiscus, and propolis) in women with uncomplicated cystitis. The authors concluded that a medical device is superior to placebo in terms of clinical effectiveness in these patients and is associated with high patient compliance. In an observational, prospective study by the same author [21], 61 women with recurrent UTIs received the medical device for 6 months. A total of 67.2%, 77.0%, and 83.6% of women reported a significant clinical improvement and quality of life during the 1-, 3-, and 6-month follow-up visits. Moreover, only seven women (11.4%) experienced at least one symptomatic episode of recurrent UTI that required the use of antibiotics.

In our present study, 81.6% of women did not require an additional consultation within seven days after the initial one. Indeed, 89.5% of those who did not receive concomitant medication (mainly antibiotics) did not require additional consultation. Only 16.5% and 1.9% of women required a second or a third consultation (the latter mainly by those with recurrent cystitis). These numbers are similar to the previous studies [15–22] showing a reduction in the number of recurrences and further consultation in comparison to placebo groups in these studies. It is interesting to note that the number of women who needed a second consultation was lower in those with no history of cystitis and who received concomitant medication (63.0%) than in those who did not receive it (92.8%). One possible explanation might derive from the fact that severe cases required intensive therapy with antibiotics. Therefore, the efficacy of the medical device in these women could be lower than it is in non-severe cases. As in other studies, we did not observe any adverse effects in this study. The recommended first-line empiric antibiotic therapy for acute uncomplicated bacterial cystitis in otherwise healthy adult nonpregnant females is a 5-day course of

an antibiotic such as nitrofurantoin, pivmecillinam, or cephalosporins. These drugs have high drug-related adverse events, such as gastrointestinal adverse events, the increase in creatinine and allergic reactions [31]. The risks of adverse drug events and potential microbiome-related events differ widely by antibiotic agent and duration [32]. In clinical practice, Utipro<sup>®</sup>Plus appears to have an important and valuable role in everyday clinical practice as a non-antimicrobial option to control and prevent UTIs and improve the quality of life in these patients [33].

## 5. Conclusions

In conclusion, the medical device containing xyloglucan, hibiscus, and propolis showed similar safety and effectiveness outcomes to prior randomized studies that were used for commercialization of this device [19,20,22,30] for the treatment of a broad spectrum of women with acute uncomplicated or recurrent UTI-like symptoms. Further long-term, prospective studies involving a large cohort of women are required to corroborate these results.

**Author Contributions:** F.B. participated in the interpretation of the results and oversaw the process as well as critically reviewed it. P.O. and E.B. were responsible for writing the manuscript. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

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