



# Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial on the Use of *Uncaria tomentosa* (Cat's Claw) for Aromatase Inhibitor-Induced Arthralgia: A Pilot Study

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## Abstract

**Introduction:** Aromatase inhibitors (AI) are widely used in adjuvant breast cancer treatment, and diffuse articular pain secondary to AI use is the most common cause of treatment discontinuation. *Uncaria tomentosa* (cat's claw) has anti-inflammatory activity and is used to treat arthrosis and arthritis. **Patients and Methods:** This prospective, single-center, double-blind, randomized, placebo-controlled phase II study analyzed 70 patients with breast cancer undergoing AI therapy with complaints of arthralgia. The patients received 100 mg of the dry extract of *Uncaria tomentosa* three times daily for 4 weeks. At the beginning and end of the study, patients answered the Brief Pain Inventory (BPI), Disability Arm, Shoulder, and Hand (DASH), Lequesne, SF-36 Quality of Life questionnaires, completed a visual analog scale (VAS) for pain, and underwent laboratory testing. **Results:** *U. tomentosa* was not more effective than the placebo. No evidence of grade 3 or 4 toxicity was found. In addition, no significant differences were seen in laboratory results or inflammatory markers between the two study groups. **Conclusion:** Dry extract of *U. tomentosa* was safe but ineffective in reducing AI-induced arthralgia compared with the placebo. Furthermore, the plant extract had no detectable anti-inflammatory activity.

**Keywords:** Aromatase Inhibitor, Arthralgia, Cat's Claw, *Uncaria tomentosa*

## 1. Introduction

Aromatase inhibitors (AIs) are widely used in adjuvant breast cancer treatment in postmenopausal women with positive hormone receptors on immunohistochemistry. AIs inhibit the enzyme aromatase, reducing estrogen production by blocking the conversion of androgen to estrogen, and are considered the most effective adjuvant hormone therapy available for these patient groups<sup>1</sup>.

Studies have demonstrated that AIs improved disease-free survival and decreased the rate of contralateral

breast cancer compared with adjuvant tamoxifen<sup>1</sup>. However, nearly 50% of patients with indications for AIs use do not adequately adhere to treatment, and the discontinuation rate of AIs use in the first year of treatment is approximately 20%. Arthralgia is the most common reason for poor adherence and discontinued treatment<sup>2</sup>.

The onset of AI-induced arthralgia occurs approximately 2 months after initiating treatment and peaks at approximately 6 months of treatment; however, this disease may recur up to 2 years after initiating

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therapy<sup>2</sup>. It is characterized by symmetrical joint pain, usually in the wrists, metacarpals, and knees. Specific diagnostic criteria for AI-induced arthralgia have been established<sup>2</sup>. The occurrence of AI-induced arthralgia affects patients quality of life and may be responsible for poor treatment adherence<sup>2</sup>.

*Uncaria tomentosa* is a plant species found in the Amazon region and is widely distributed in South and Central America. This species belongs to the family Rubiaceae and subfamily Cinchonoideae, and its popular name, “cat’s claw”, is derived from the resemblance of the plant’s thorns to claws. This plant species was used by the Incas for centuries to treat arthritis, arthrosis, viral infections, cancer, and other inflammatory conditions because its active metabolites, including pentacyclic and indole oxindole alkaloids and quinovic acid glycosides, have antioxidant, immunomodulatory, antineoplastic, anti-inflammatory, and antiviral activities<sup>3-4</sup>. The anti-inflammatory effects of *U. tomentosa* may be related to the decreased expression of transcription factor NFκ-beta, which decreases tumor necrosis factor (TNF) levels, leading to increased anti-inflammatory activity in cells<sup>3</sup>.

The primary objective of this study is to evaluate arthralgia reduction by *U. tomentosa* dry extract in patients with breast cancer in adjuvant treatment or chemoprophylaxis of mammary carcinoma *in situ* who developed arthralgia during AI use or whose previous arthralgia symptoms intensified with AI use, using specific questionnaires to assess joint pain and quality of life.

The secondary objectives were to evaluate the drug’s safety and to determine the relationship between arthralgia and inflammatory markers.

## 2. Materials and Methods

### 2.1 Study Design

This prospective, single-center, double-blind, *Uncaria tomentosa* dry extract versus placebo, phase II study included patients using AI who developed arthralgia during cancer treatment or whose previous symptoms of arthralgia intensified with AI use.

This study was approved by the Research Ethics Committee of the Instituto Brasileiro de Controle do

Cancer (IBCC). Patients were recruited and evaluated in the IBCC outpatient clinics.

### 2.2 Inclusion and Exclusion Criteria

Inclusion criteria were postmenopausal women with a history of breast cancer and/or carcinoma *in situ*, treated in IBCC outpatient clinics, with positive hormone receptors on immunohistochemistry, undergoing adjuvant AI and/or chemoprophylaxis for at least 2 months, who developed moderate or severe arthralgia after initiating AI treatment or whose arthralgia worsened by 40% or with a score  $\geq 5$  on the Brief Pain Inventory (BPI) questionnaire.

Exclusion criteria were women diagnosed with or treated for diseases that cause arthralgia such as rheumatoid arthritis, arthrosis, or fibromyalgia, or arthralgia before using anastrozole, pregnant or breastfeeding women, transplanted patients, and patients with anemia at the time of recruitment.

Patients who failed to take the medication for a 48-hour period or developed severe adverse events from drug therapy were excluded from the study.

### 2.3 Study Procedures

After patients signed the consent form, their clinical histories, analgesic use, and physical activity were evaluated. During the same visit, serum biological samples were collected for laboratory tests, and pain levels were assessed using the BPI, Lequesne, Disability Arm, Shoulder, and Hand (DASH), and SF-36 Quality of Life questionnaires.

Treatment lasted 4 weeks. Between weeks 2 and 3, treatment adherence and side effects were evaluated by phone. At week 4, patients had a new consultation with the investigator to collect biological material for laboratory testing and to reassess pain and quality of life with the questionnaires.

A daily record of medication use, physical activity, and improvement of pain or other symptoms was provided to each patient at the first visit and collected by the investigator at the end of the study.

### 2.4 Efficacy Parameters

The efficacy parameters in this study were classified using five tools:

- Brief Pain Inventory (BPI)<sup>5</sup>
- Visual analog scale (VAS) for pain<sup>6</sup>
- Lequesne (osteoarthritis)<sup>7</sup>
- Disabilities of the Arm, Shoulder, and Hand (DASH)<sup>8</sup>
- SF-36 questionnaire for assessing the quality of life<sup>9</sup>

## 2.5 Drug Therapy

The drug used was *U. tomentosa* dry extract in manipulated 100-mg capsules standardized to 5.0 + 0.5 % total alkaloids expressed as mitraphylline (Lot TYC160110, manufactured on January 10, 2016 and valid until January 9, 2019).

The placebo was manipulated in 100-mg capsules identical to the *U. tomentosa* capsules manufactured using cornstarch and food coloring.

The dosage was 100-mg tablet of the dry extract three times daily for 30 days, as recommended in the package insert.

Treatment adherence was evaluated by counting the number of capsules in the returned packages. For this purpose, the patients were instructed to return the packages to the investigator at the end of the study and the packages were then returned to the pharmacy.

## 2.6 Laboratory Tests

Whole blood (15 mL) was collected from each patient at the first and last visits. The blood was transferred to two collection tubes containing EDTA and two collection tubes containing cobalt gel. Laboratory analyses included a complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, estradiol, and vitamin D. All tests were performed in duplicate at the Laboratory of Clinical Analysis of FMABC following good clinical practices.

The two patient groups were biochemically compared using the Glasgow Prognostic Score (GPS)<sup>10</sup> based on serum CRP and albumin levels and neutrophil-lymphocyte ratios. The first classification considered patients with a low risk of systemic inflammation as normal CRP (<10 mg/L) regardless of albumin level; patients with an intermediate risk as high CRP (>10 mg/L) and normal albumin (5 g/L); and patients with a high risk as high CRP (>10 mg/L) and hypoalbuminemia (<3.5 g/L). The second classification using the lymphocyte

ratio was determined by dividing the total number of neutrophils by the total number of lymphocytes.

## 2.7 Adverse Events

Patients were asked to report adverse events to the investigator and were scored using the toxicity criteria developed by the National Cancer Institute, version 2.0<sup>11</sup>

## 2.8 Statistical Analysis

The sample size was calculated by considering an intergroup difference in arthralgia reduction of 40%, type 1 error of 0.05, and power of 80%. The analysis predicted the inclusion of 35 patients per group.

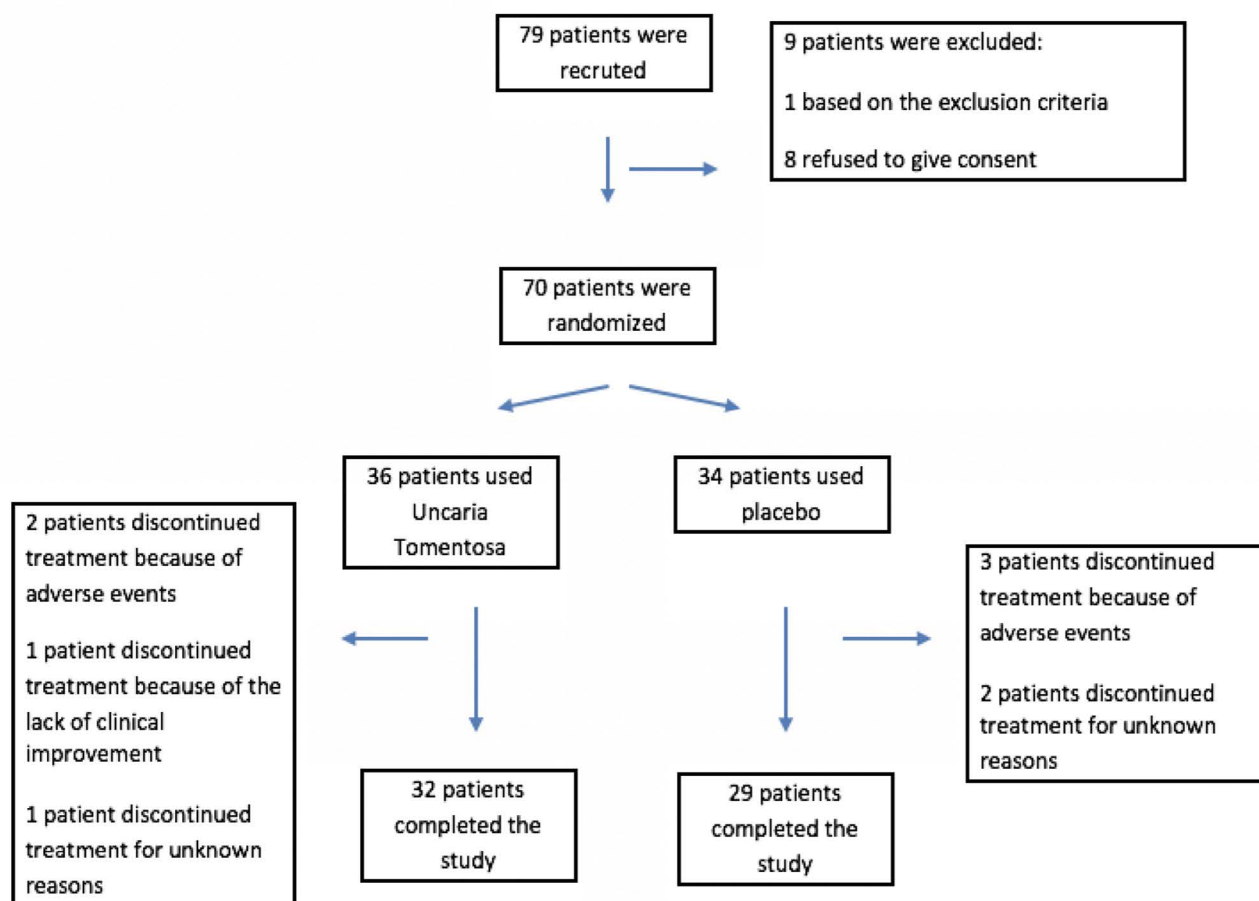
We evaluated associations between continuous and discrete variable through the ANOVA test. Associations between discrete variables were evaluated by the Chi-square test or the Fisher Exact test.

All statistical analyses, concerning questionnaire data, were conducted using the NCSS statistical package (<https://www.ncss.com/software/ncss/>).

## 3. Results

### 3.1 Study Population

Seventy patients were randomized from October 1, 2016, to March 1, 2017 (Figure 1). The mean age was 59.2 years, all patients were women, and 58% were Caucasian. Clinical stage I was observed in 29.8% of patients, and luminal subtype B was the most prevalent on immunohistochemistry (49.3%). Most patients (66.3%) had undergone chemotherapy, and of these, 51.9% had undergone taxane therapy. Anastrozole was used in 98.7% of patients and exemestane was used in one patient (1.3%). The mean AI therapy length was 20.58 months (2-96 months). Of the 70 patients, 13 (16.8%) performed aerobic physical activity, and 49 (70%) used analgesics to manage arthralgia. The most common painful regions were the knees (57; 81.42%), spine (45; 64.28%), metacarpus (43; 61.42%), and shoulders (34; 48.57%). The mean BMI was 29.73±5.69. The patients' general characteristics are presented in Table 1.



**Figure 1.** Study flowchart.

### 3.2 Evaluation of the Questionnaires and Hematological and Inflammatory Parameters

*U. tomentosa* dry extract was not more effective than the placebo when evaluated using the questionnaires. On the VAS for assessing pain intensity, the placebo was more effective than the dry extract ( $p = 0.02$ ) (Table 2). All patients who completed the study answered the questionnaires.

Similarly, no significant differences were seen in inflammatory or hematological markers between the dry extract and the placebo (Tables 3 and 4). Laboratory analysis was conducted for only 50 patients (25 in the placebo group and 25 in the control group) because some patients who completed the study had their second blood sample collected more than 3 months after starting the drug or placebo treatments.

Use of *U. tomentosa* in this patient group was safe, and no cases of grade 3 or 4 toxicity occurred (Table 5). Adverse events were analyzed in 32 patients who underwent AI therapy and completed the study, two patients who discontinued AI therapy because of adverse events, 29 patients who used a placebo and completed the study and three patients who discontinued placebo treatment because of adverse events.

## 4. Discussion

Several hypotheses may explain the etiology of AI-induced arthralgia, particularly the hypothesis that AI intensifies low estrogen levels during menopause.

Estrogen may exert antinociceptive activity. Higher estrogen levels suppress inflammatory cytokine production, whereas lower levels increase cytokine production<sup>12-13</sup>. In addition, estrogen

deficiency increases cartilage turnover, thereby reducing its protective capacity<sup>2</sup> the figure has been much higher in subsequent case series. There is concern that these symptoms are significant and may affect compliance and thus the overall efficacy of treatment. It is therefore extremely important that we evaluate this syndrome with a view to gaining more information regarding its clinical features and possible aetiological mechanism. The potential aetiological mechanisms and evidence for aromatase inhibitor-induced arthralgia (AIA).

These results and *U. tomentosa's* reported anti-inflammatory activity for chronic inflammatory

diseases, including rheumatoid arthritis and arthrosis in phase II studies<sup>14</sup>, stimulated the investigation of this plant extract's efficacy in treating AI-induced arthralgia.

As previously reported in an uncontrolled study conducted by our research group<sup>15</sup>, no detectable effect of *U. tomentosa* was found on the inflammatory markers studied, including ultra-sensitive CRP, the ESR, or the GPS. Results from our previous study found no significant differences in serum levels of IL6, IL1, TNF $\alpha$ , or alpha-1-glycoprotein between, before or after *U. tomentosatreatment*<sup>15</sup>. Mur et al.<sup>14</sup> found a modest reduction of arthralgia in patients

**Table 1. Patient demographics**

	DRUG (n = 36)	PLACEBO (n = 34)
<b>Age, mean (range)</b>	59.2 (33–79)	60.79 (43–80)
<b>BMI, mean (range)</b>	28.6 (20–45)	30.88 (46–23)
<b>Use of AI (months), mean (range)</b>	23.97 (72–2)	17.5 (96–2)
<b>N (%)</b>	<b>Race</b>	<b>Race</b>
<b>Caucasian</b>	21 (58%)	24 (70.5%)
<b>Mixed</b>	9 (25%)	4 (11.7%)
<b>Black</b>	5 (13.8%)	6 (17.6%)
<b>Asian</b>	1 (2.7%)	0 (0%)
<b>N (%)</b>	<b>Cancer staging</b>	<b>Cancer staging</b>
<b>Carcinoma in situ</b>	0 (0%)	1 (2.9%)
<b>I</b>	9 (25%)	14 (41%)
<b>II</b>	16 (44.4%)	11 (32.35%)
<b>III</b>	11 (30.5%)	8 (23.5%)
<b>N (%)</b>	<b>Immunohistochemistry</b>	<b>Immunohistochemistry</b>
<b>Luminal A</b>	13 (36.1%)	10 (29.4%)
<b>Luminal B</b>	21 (58.3%)	17 (50%)
<b>Luminal hybrid</b>	2 (5.5%)	7 (20.5%)
<b>Previous chemotherapy</b>	28 (77.7%)	23 (67.6%)
	<b>Before treatment</b>	<b>After treatment</b>
<b>Previous chemotherapy with taxanes</b>	21 (58.3%)	19 (55.8%)
<b>Previous radiotherapy</b>	31 (86.1%)	29 (85.2%)
<b>Physical exercise</b>	6 (16.6%)	7 (20.5%)
<b>N (%)</b>	<b>Current treatment with AI</b>	<b>Current treatment with AI</b>
<b>Anastrozole</b>	35 (97.2%)	34 (100%)
<b>Others</b>	1 (2.7%)	0 (0%)

**Table 2. Questionnaire evaluation**

	Before treatment			After treatment		
	Drug	Placebo	p-value	Drug	Placebo	p-value
SF36 (functional capacity)	25 ± 26.9	30 ± 24.7	0.93	40 ± 23.8	37.5 ± 28.1	0.72
SF36 (physical limitations)	25 ± 28.62	0 ± 35.8	0.85	25 ± 37.04	50 ± 43.75	0.46
SF36 (pain)	31 ± 13.15	36.5 ± 18.5	0.062	32 ± 21.3	41.5 ± 26.1	0.07
SF36 (overall health status)	76.5 ± 24.2	86 ± 25.1	0.35	62 ± 19	63.5 ± 26.2	0.91
SF36 (vitality)	40 ± 19.86	50 ± 24.1	0.11	45 ± 22.3	55 ± 21.05	0.096
SF36 (social aspects)	56 ± 31.8	75 ± 29.3	0.04	62.5 ± 30.4	75 ± 29.5	0.21
SF36 (emotional aspects)	33.79 ± 39.70	33 ± 43.2	0.61	66 ± 38.9	66.3 ± 43.3	0.52
SF36 (mental health)	54 ± 29.9	64 ± 21.6	0.31	64 ± 25.5	68 ± 25.3	0.68
Lequesne	15 ± 6.2	15.25 ± 5.5	0.87	12 ± 6.2	10 ± 5.6	0.4
DASH (disabilities)	43.75 ± 23.90	33.12 ± 24.70	0.97	25 ± 25.37	23.75 ± 27.10	0.63
DASH (pain)	62 ± 25.5	62 ± 22.8	0.87	48 ± 28.7	54 ± 28.6	0.69
BPI (pain severity)	6.5 ± 1.39	6.375 ± 8.3	0.41	6.5 ± 7.3	5.25 ± 2.7	0.08
BPI (pain interference)	5.75 ± 7.5	5 ± 10.1	0.83	3.4 ± 7.8	3.55 ± 3.1	0.3
VAS	8 ± 2.1	8 ± 2.1	0.71	8 ± 2.74	5 ± 3.1	0.02

**Table 3. Laboratory analysis**

	Before treatment			After treatment		
	Drug	Placebo	p-value	Drug	Placebo	p-value
Vitamin D	31 ± 9.03	29 ± 11.2	0.85	31.1 ± 9.8	24 ± 10.6	0.5
Estradiol	6 ± 4.7	6 ± 0.45	0.21	6 ± 3.7	6 ± 1.5	0.36
Erythrocyte sedimentation rate	21 ± 24.1	23.5 ± 13.7	0.76	13 ± 18.2	19 ± 17.5	0.49
Albumin	4.2 ± 0.22	4.2 ± 0.29	0.84	4.3 ± 0.3	4.3 ± 0.3	0.65
C-reactive protein	6 ± 7.86	6 ± 3.6	0.43	6 ± 1.8	6 ± 1.9	0.59
Hemoglobin	12.7 ± 1.2	13.3 ± 0.9	0.21	12.6 ± 1.1	13 ± 10	0.28
Neutrophil-lymphocyte ratio	1.89 ± 0.97	1.93 ± 0.85	0.2	1.93 ± 0.81	1.62 ± 0.69	0.35
Platelets	225 ± 57.68	220 ± 46.5	0.34	234.5 ± 59.6	213 ± 66.3	0.08

**Table 4. Glasgow Prognostic Score rating**

	Glasgow Prognostic Score			
	Before treatment		After treatment	
	Drug	Placebo	Drug	Placebo
Low risk	24 (88%)	24 (92.3%)	23 (92%)	22 (88%)
Intermediate risk	3 (11.1%)	2 (7.29%)	2 (8%)	3 (12%)
High risk	0	0	0	0
Total	27 (100%)	26 (100%)	25 (100%)	25 (100%)

with rheumatoid arthritis treated with *U. tomentosa* but detected no significant changes in CRP or ESR in patients treated with *U. tomentosa* versus the placebo. Similarly, Araujo et al.<sup>16</sup> who underwent a treatment regimen known as FAC (Fluorouracil, Doxorubicin, Cyclophosphamide) observed no significant changes in IL-6 or lymphocyte subpopulation levels in patients with breast carcinoma receiving adjuvant chemotherapy combined or not with *U. tomentosa*. The lack of a beneficial effect of *U. tomentosa* on AI-induced arthralgia in our study may be due to the

**Table 5. Adverse Events**

PATIENTS USING DRUG (n = 34)					
ADVERSE EVENT	SEVERITY OF THE EVENT				
	All grades	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Nausea	1 (2.94%)	1	0	0	0
Vomiting	0	0	0	0	0
Abdominal pain	1 (2.94%)	1	0	0	0
Abdominal distension	0	0	0	0	0
Constipation	1 (2.94%)	1	0	0	0
Epigastralgia	0	0	0	0	0
Diarrhea	2 (5.88%)	2	0	0	0
Intestinal subocclusion	1 (2.94%)	1	0	0	0
Lower limb edema	1 (2.94%)	1	0	0	0
Neuropathy	1 (2.63%)	1	0	0	0
Allergic reaction	0	0	0	0	0
PATIENTS USING PLACEBO (n = 32)					
ADVERSE EVENT	SEVERITY OF THE EVENT				
	All grades	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Nausea	3 (9.37%)	0	3	0	0
Vomiting	3 (9.37%)	2	1	0	0
Abdominal pain	1 (3.12%)	1	0	0	0
Abdominal distension	1 (3.12%)	1	0	0	0
Constipation	0	0	0	0	0
Epigastralgia	1 (3.12%)	0	1	0	0
Diarrhea	3 (9.37%)	2	1	0	0
Intestinal subocclusion	0	0	0	0	0
Lower limb edema	1 (3.12%)	1	0	0	0
Neuropathy	2 (6.25%)	2	0	0	0
Allergic reaction	2 (6.25%)	2	0	0	0

lack of a significant effect on inflammatory markers in the treated patients. In addition, as described above<sup>2</sup> the etiopathogenesis of AI-induced arthralgia appears to be multifactorial, and inflammation is one of several causes.

No significant changes were found in laboratory parameters in patients treated with *U. tomentosa* compared with the placebo group. Moreover, patients receiving *U. tomentosa* showed no grade 3 or 4 toxicity. Consistent with our previous study<sup>15</sup>, *U. tomentosa* was safe at the doses used in this study.

## 5. Conclusion

In conclusion, using *U. tomentosa* dry extract was safe but not more effective than the placebo in treating AI-induced arthralgia; therefore, use of this extract cannot be recommended for this purpose.

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