

**Original Article**

**SYNTHETIC PRODUCT ILLEGALLY SOLD IN BRAZIL AS A MEDICINAL HERBAL PRODUCT:  
CHEMICAL ANALYSIS AND THE PATIENTS MEDICATION EXPERIENCE**

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**ABSTRACT**

**Objective:** To analyze a product illegally sold as herbal medicine acquired and used by a patient and to understand the reasons that led the patient to use this product.

**Methods:** The chemical analysis was performed by thin layer chromatography (TLC) and mass spectrometry (MS) analysis with a direct infusion with a Bruker Daltonics UltroTOF-Q, in positive mode. A qualitative interview was conducted with the patient. The data obtained were submitted to thematic analysis.

**Results:** Chemical analysis confirmed the presence of piroxicam and orphenadrine, and the complete absence of a natural product. The qualitative study revealed three themes: previous experience with the disease and the use of medicines, feelings about the care provided by health professionals, and the patient's solution.

**Conclusion:** The commercial availability of this kind of product raises concerns about safety and demonstrates the necessity for more intensive surveillance by health authorities. In addition, the present study showed the need for a patient-centered practice and the understanding of medication experience to provide effective care to patients who use medicines to preserve them from unsafe products.

**Keywords:** Herbal medicine adulteration, Chemical analysis, Medication experience, Qualitative research

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**INTRODUCTION**

In recent decades, the use of dietary supplements and natural drugs has increased considerably. Herbal medicines have become very common in the treatment of a variety of chronic diseases (diabetes, arthritis and others) [1-4], and patients use these medicines without a prescription, and with neither pharmaceutical nor medical care. Many individuals are taking control over their health, replacing allopathic drugs with natural therapy [5-7]. According to the experience medication concept exerting control over their medications is a common practice in patients who take medicines chronically [8]. Knowledge about patient experience and specifically medication experience should be used by health care professionals who intend to have an effective practice and to provide more benefits to patients [9, 10]. Furthermore, when dealing with patients being treated for chronic diseases and using medicinal plants, the professional must also carry over into another field of knowledge: pharmaceutical sciences, herbal medicine and pharmacognosy. This is because "the false belief that natural is better than chemical" or "natural and therefore free of risk" can expose patients to unnecessary risks [11, 12].

In general, medicinal plants are used without a specific pharmacological target. But when they show strong activity, the pure isolated compound from the plant must be used, since efficacy and safety are required [6, 7, 13, 14]. Although the safety problem (toxicity) of herbal medicinal products has been revised, drug interactions, appropriate pharmaceutical preparations, and other topics are neglected [11]. In addition, the adulteration of herbal medicines and their availability on the internet without oversight is a serious concern [5, 11, 15]. A systematic review on the adulteration of Chinese medicinal herbs with synthetic drugs demonstrated a wide distribution of adulterated drugs on all continents except Africa [11]. Subsequently, the sale of this kind of product was also described in South America [5].

To contribute to generating knowledge in this field, this paper has two aims: *i*) to describe the chemical evaluation of a product illegally sold in Brazil as an herbal product, known as harp 100 and *ii*) to evaluate a patient's experience with the treatment of a chronic disease, including the use of harp 100 as self-medication.

**MATERIALS AND METHODS**

**Chemical evaluation of the product**

**Analysis by thin layer chromatography**

A capsule of a product described as natural (harp 100 mg) was extracted with methanol P. A. (10 ml) for 15 in an ultrasound bath. The filtrate was concentrated, and the residue was solubilized in methanol (1 ml). The extract was first analyzed according to its TLC profile and compared to those accordingly described for *Harpagophytum procumbens* in the literature [11].

Other TLC plates were compared to some readily available analgesic and/or anti-inflammatory drugs (pharmaceutical grade piroxicam, indomethacin, dipyron sodium, caffeine, diclofenac sodium, and ketorolac tromethamine). Both analyses were performed by TLC (silica gel, 20 µl).

The first analysis was performed in AcoEt: MeOH: H<sub>2</sub>O (77:15:8) and revealed with vanillin/sulfuric acid to check for plant metabolites [16], while the analysis for the pharmaceutical patterns were eluted with ethyl acetate: acetic acid: water (100:22:26) and revealed with UV light and Dragendorff solution. With the purpose of isolating the chemical constituents, preparative TLC was developed under the same conditions.

**Analysis by ultraviolet**

The ultraviolet spectra of the samples obtained from preparative TLC and the piroxicam pattern were developed using a Thermo

Scientific Genesys 10s UV-Vis spectrophotometer. The samples and pattern were analyzed in methanol in the 200-450 nm range.

#### Analysis by HPLC-DAD/MS-ULTRO-TOF-Q

The capsule was solubilized in MeOH: H<sub>2</sub>O 7:3 (500 µg/ml) and filtered through a 0.45 µm filter. This solution was used for injection into the HPLC-DAD apparatus and after 10-fold dilution was used for MS analysis. The product was analyzed on a binary solvent HPLC system (LC-20AD, Shimadzu), coupled to a diode array detector (SPD-M20A, Shimadzu), operating at 314 nm. The analytical column used was a C-18 Shimadzu Shim-pack (250 mm x 4.6 mm ID, 5 particle mmol) and a guard column (4 cm x 3 mm) with the same stationary phase. The mobile phase was composed of H<sub>2</sub>O (A) and MeOH (B), both with 1% acetic acid, at a flow rate of 0.8 ml/min. The analysis was performed with a linear gradient system: 0.01-10 min 5-100% (B), followed by a 10-15 min return to the initial conditions and column restabilization. The solvents used were HPLC grade (Vetec) and Milli-Q water (Millipore).

MS analysis was performed by direct infusion with an UltroTOF-Q Bruker Daltonics, in the positive mode, flow of 10 µl min<sup>-1</sup>. Calibration was performed with Na<sup>+</sup>TFA (trifluoroacetic acid sodiated). Observed peaks were compared with standards to confirm the identification, piroxicam 20 mg-medley and DORFLEX® sanofi-aventis. The protonated compounds were fragmented with an energy of 25eV.

#### Accessing the patient's medication experience

##### Data collection

A semi-structured interview was conducted with the patient who used the harp 100 product. This data collection method provided a deep description of the patient's illness and medication experience. The data was recorded and transcribed. The patient's name was omitted to protect her identity.

##### Data analysis

A thematic analysis of the data was performed by a researcher. The themes that emerged from this step were presented and discussed with the other researchers, applying the collaborative analysis method [17, 18].

This study was approved by the ethics committee on research involving human subjects of the Federal University of São João Del Rei, Brazil.

## RESULTS AND DISCUSSION

### Chemical analysis

The preliminary analysis by TLC was performed with the purpose of observing the fingerprint of some medicinal plants used to treat arthritis [19]. The TLC plate was revealed by vanilla/sulfuric acid, and the profile (fig. 1) was in disagreement with the presence of an herbal medicinal plant [16] used in the treatment of degenerative disease (N14). Then, further TLC was developed, suitable for revealing amine compounds, with the purpose of detecting synthetic anti-inflammatory compounds used as an adulterant [5, 11]. Dragendorff solution was used to reveal the preparative TLC and additional ultraviolet analysis was also performed (fig. 2). Orange spots were observed relative to the presence of two or three substances in the product (1), but an accurate analysis was performed by HPLC-DAD-MS-ULTRO-TOF-Q.

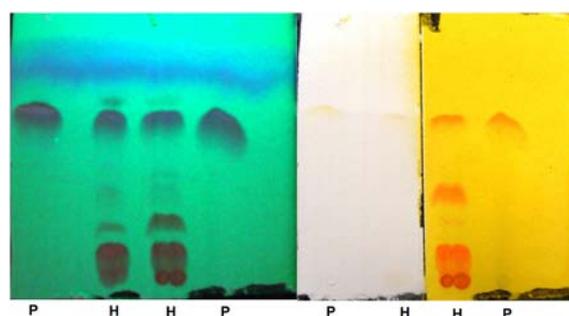


Fig. 1: Left side: piroxicam (P) and harp (H) on the ultraviolet light at 256 nm. On the right side: TLC plate was revealed by vanilla/sulfuric acid (left) and no spot was observed. Dragendorff solution was also used (right), and piroxicam (P), and other nitrogen compounds were observed in the harp (H)

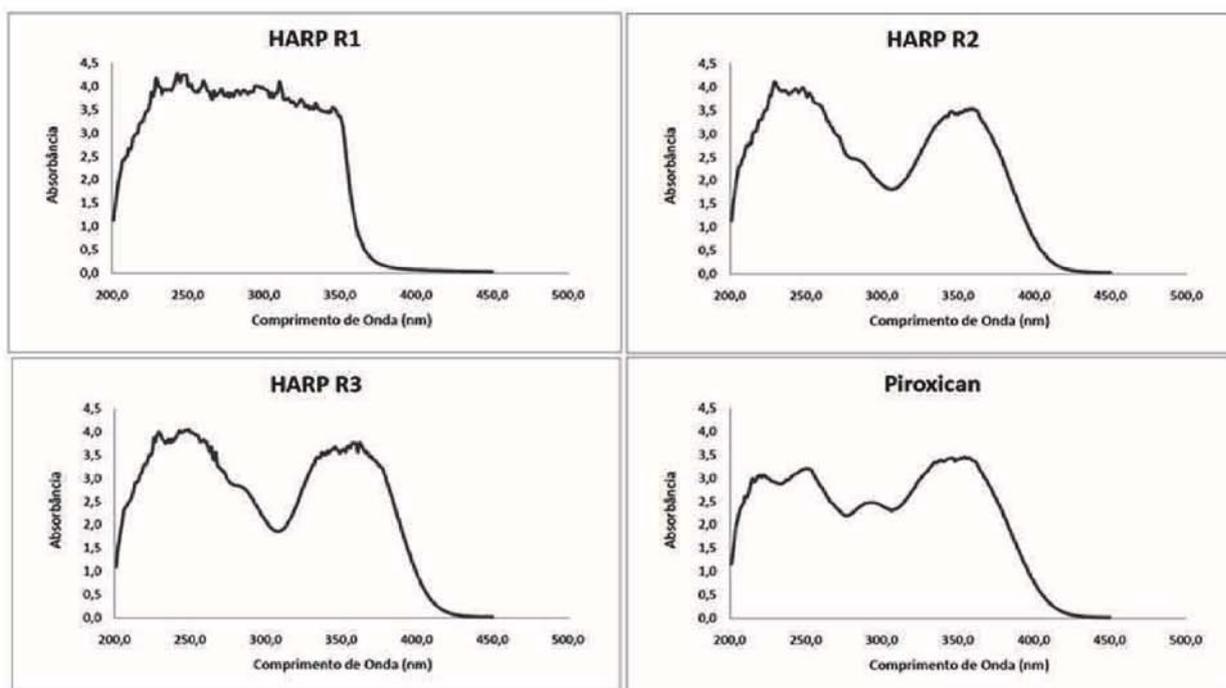
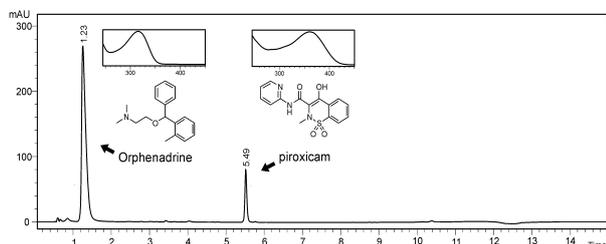


Fig. 2: Ultraviolet spectra of piroxicam and of the substances obtained by preparative thin layer chromatography of harp (R1, R2 and R3 according to retention factor (Rf) found for the spots in the fig. 2, from start to front)

MS injection showed two main peaks  $m/z$  270.1851 ( $C_{18}H_{24}NO^+$ , error 2.5 ppm), compatible with orphenadrine and MS  $m/z$  332.0716 ( $C_{15}H_{14}N_3O_4S^+$ , error 3.3 ppm) compatible with piroxicam. After the observation of the two peaks, the sample was re-injected in the HPLC and compared with standards confirming the presence of these two compounds on capsules. (fig. 3).



**Fig. 3: Chromatogram of harp 100 mg on HPLC-DAD-MS-ULTRO-TOF-Q (Highlighted the ultraviolet spectra)**

### The patient's medication experience

Immediately after the confirmation of adulteration, the patient was notified and interviewed with the purpose of understanding the personal reasons and decision-making process regarding the use of an illegal product.

The patient has an academic career in the exact sciences. Despite this high level of education, she reported that she had made the choice of using the product sold as natural thinking that "it wouldn't have adverse effects, being an herbal medicine and not having any chemical involved" (excerpt from the interview). Medicinal plants and herbal medicines have been presented by the media as alternative therapeutic resources without adverse effects, and devoid of any toxicity or contraindications [11, 13]. This concept seems to have influenced the patient's decision to use harp 100.

Additionally, her previous experience with drugs commonly used to treat her chronic disease rheumatoid arthritis, a clinical condition associated with chronic pain [20]-is very negative. Since the patient had experienced the illness of a family member with the same condition in the past and observed her treatment, she had concerns regarding the adverse effects of glucocorticoids and other medicines. This previous negative experience influenced her behavior regarding pharmacotherapy.

*"(.) My knowledge was just from watching my mom's treatment. I knew what she took. For example: 'Chloroquine. Ah! It's bad for the vision. I'm not going to take that'. [Simulating her decision-making process about the pharmacotherapy in the past]" (excerpt from the interview).*

This relationship between previous knowledge about medicine and the patient's decisions about her treatment was also identified by Shoemaker and Ramalho de Oliveira [8] leading to the creation of the experience medication concept. The researchers identified that a healthcare professional who seeks to resolve problems related to medicines needs to use the patient's medication experience to evaluate and make interventions [21]. It is recommended that this concept and its use in clinical practice are incorporated into the curriculum of health professionals who are co-responsible for patient pharmacotherapy [9, 21].

Another important factor in the decision to self-manage her pharmacotherapy revealed by the patient refers to her relationship with health professionals. She said that the professional who assisted her at the beginning of her treatment was technically very competent. However, the patient complained that the psychosocial aspects of her illness were not considered. The lack of a patient-centered approach made the patient feel unrecognized in terms of her feelings about pharmacotherapy and discouraged her from following professional recommendations.

Toye and collaborators [22] conducted a systematic review of 77 qualitative studies on the experience of patients who live with

musculoskeletal pain. The theme "negotiation with the health system" comes up as one of the six main themes identified by these researchers in the meta-synthesis. They affirm that a patient wishes to be valued as a person in the health system, and not just as a health problem to be solved and diagnosed. "I also need to be treated as more than just a body. This is central to the therapeutic relationship, not an adjunct" [22]. In the same way, Mohammed, Moles and Chen [23] conducted a systematic review with a meta-synthesis of 34 qualitative studies on patient experiences with medicine and found that the absence of an established patient-practitioner therapeutic relationship had a negative impact on patient beliefs about medicine and medicine-taking behavior.

*"She is an excellent health professional, but I gave up on her. (.) She controlled my mom's arthritis; it was fantastic. There is nothing that I can tell you: 'That health professional is bad.' She is just: the treatment is this, and you need to do this." (excerpt from the interview).*

The patient's statement shows a conflict between health based on biomedical evidence, which is based on the Cartesian model, and a person-centered practice, which is humanist with a biopsychosocial perspective. As Bensing [24] found the challenge of the health professional is to pursue the approach and the integration of these two paradigms for the benefit of the patient.

Therefore, the patient stated that she conducted her therapy based on her own knowledge. She delayed the introduction of chloroquine, and she preferred not to use corticosteroids. She mostly tolerated the pain interspersed with some periods of non-steroidal anti-inflammatory use. These attitudes and behaviors are usually observed among medicine users after they develop experience and knowledge about the effects of the medicines in their body [8]. Mohamed, Moles and Chen [23] emphasize that patients usually make decisions to manipulate their prescribed doses or regimen to manage intolerable effects of a medicine and its interference in daily life.

However, the debilitating nature of the disease associated with its management not supported by a professional resulted in suffering and activity restriction for this patient. "The way I am living with pain, if you give me poison and say that it is good, I will take it." (excerpt from the interview). Consequently, she began a search for other treatment possibilities. An acquaintance told her about harp 100, which was acquired by this person. This illegal product, unlike other herbal medicinal products available on the pharmaceutical market, promoted rapid pain relief and a powerful analgesic effect, which were responsible for the total adherence to treatment of the patient through self-medication. However, over the course of time, the patient suspected the high effectiveness of the product and requested an evaluation of its chemical composition, and found out about the adulteration. With feelings of regret and fear to keep using the product due to the presence of a synthetic drug (anti-inflammatory), the patient stopped the treatment and shared her discovery with the people who suggested using the product.

*"Now that I know that it's bad, that it has a lot of things inside, that it's not what they say that is, of course, I am not going to take it anymore. However, it was good, it was a relief for pain, it certainly was." (excerpt from the interview).*

Therefore, the patient's medication experience revealed in this study is composed of an erroneous belief in the safety of natural products, previous experience with a family with a similar disease and treatment and problems in with the patient-health professional relationship. Understanding these aspects of medicine use in a patient's daily lives is essential for professionals that are co-responsible for the patient's pharmacotherapy in order to have an effective clinical practice. Medication experience is one way to identify drug-related problems, which need to be the target of pharmaceutical interventions. This is essential knowledge in direct patient care, i.e. to ensure that the medicines used are indicated, effective, safe, and convenient [21].

### CONCLUSION

This is not the first product described in Brazil as powerful and fast in pain alleviant, and will not be the last. The commercial availability of this kind of product raises concerns about safety, and demonstrates the necessity for more intensive surveillance by

health authorities, since this product was forbidden in 2010, but it remains available on the internet.

The present study showed the need for a patient-centered practice by health professionals, with the aim of understanding subjective experiences and providing information regarding their concerns and fears about pharmacotherapy, thus ensuring safety and successful treatment.

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#### CONFLICTS OF INTERESTS

All authors have none to declare

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