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Illegal market of products for treatment of chronic pain: a case study

Comércio ilegal de produtos para tratamento da dor crônica: estudo de caso

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ABSTRACT

The present study reports a case through an analysis and discussion on legal and phytochemical fields on a product marketed for treatment of chronic pain (Natural Life Harp capsules 100 mg). Analyses were performed from legal aspect, besides the product phytochemical screening and qualitative analysis of the drugs (steroids/anti-inflammatory). In the legal context, the standards set by the National Health Surveillance Agency (Anvisa) were consulted. During the phytochemical screening were performed reactions for identification of saponins, steroids and triterpenoids (Liebermann-Burchard), anthraquinones (Born Traeger), flavonoids (Shinoda), tannins and polyphenols (ferric chloride), carbohydrates (Fehling) and alkaloids (Drangedorf, Mayer and Bertrand) in comparison with a standard sample of *Uncaria tomentosa* held by merchants as a constituent of formulation. Samples and standards of anti-inflammatory steroids were diluted in hexane:ethyl acetate (8:2) then applied on sheet chromatography of silica gel and eluted with dichloromethane: methanol (95:5). At the end, it was sprayed on the plate a solution of ceric sulfate for better visualization under UV light. Product without registration in Brazil, and outside the standards set for labeling and packaging by Anvisa, was considered illegal. Phytochemical screening revealed the absence of all secondary metabolites analyzed in contradiction to that observed in plant extract of *Uncaria tomentosa*. This revealed the presence of anthraquinones, tannins and polyphenols. Regarding presence of synthetic drugs, the results indicated the presence of diclofenac and piroxicam. Thus the evaluated product was considered as adulterated and out of the legal requirements, confirming the need for strict monitoring to protect the health of the population.

Keywords: **Cat's Claw; Uncaria; Pharmaceutical Trade; Anti-Inflammatory Agents**

RESUMO

O presente estudo relata um caso através de uma análise e discussão nos âmbitos legal e fitoquímico sobre um produto comercializado para tratamento da dor crônica (Natural Life Harp cápsulas de 100mg). Realizaram-se análises do aspecto legal, triagem fitoquímica do produto e análise qualitativa de fármacos (corticoides/anti-inflamatórios). No âmbito legal, consultaram-se as normas estabelecidas pela Agência Nacional de Vigilância Sanitária (Anvisa). Durante a triagem fitoquímica realizaram-se reações para identificação de saponinas, esteroides e triterpenoides (Liebermann-Burchard), antraquinonas (Born Traeger), flavonoides (Shinoda), taninos e polifenóis (cloreto férrico), carboidratos (Fehling) e alcaloides (Drangedorf, Mayer e Bertrand) em comparação com uma amostra padrão de *Uncaria tomentosa,* declarado pelos comerciantes como constituinte da formulação. Amostras padrões de corticoides e anti-inflamatórios foram diluídas em hexano:acetato de etila (8:2), em seguida, aplicadas em folhas de cromatografia de sílica-gel e eluídas em diclorometano:metanol (95:5). Ao final, aspergiu-se sobre a placa solução de sulfato cérico para visualização em luz ultravioleta. Sem registro no Brasil e fora dos padrões definidos para rotulagem e embalagem pela Anvisa, o produto encontrou-se em situação ilegal. A triagem fitoquímica revelou a ausência de todos os metabólitos secundários analisados, em contradição ao observado no extrato vegetal de *Uncaria tomentosa*. Este revelou a presença de antraquinonas, taninos e polifenóis. Quanto à presença de fármacos sintéticos, os resultados apontaram a presença de piroxicam e diclofenaco sódico. Assim, o produto em avaliação mostrou-se fora dos requisitos legais e adulterado, confirmando a necessidade de uma fiscalização rígida para proteger a saúde da população.

Palavras-chave: **Unha-de-Gato; Uncaria; Comercialização de Medicamentos; Anti-Inflamatórios**

INTRODUCTION

Herbal medicines are increasingly popular in many countries, in part due to recognition of its value in traditional medical practices around the world as well as its low cost. In recent decades, the use of natural medicines have increased and many people are replacing synthetic drugs by herbal medicines, most often due delay of effect, not perception of expected effect, or erroneous popular notion that "if it is natural, it is risk free". (MIRANDA et al., 2011).

Among diseases that require alternative treatment are patients with chronic pain. This is a public health problem that causes personal and social damage. Epidemiological studies of chronic pain in Brazil and the rest of the world are scarce, especially regarding non-specific pain, in populations not linked to health services. National studies show prevalence of chronic pain between 20 and 50% of population (SÁ et al., 2008; KRELING et al., 2006). Studies in developed countries show prevalence of chronic pain between 19 and 40% of population (PICAVET et al., 2003; ERIKSEN et al., 2003). Pain is considered chronic when it is continuous or recurrent and lasts longer than 3 months. Chronic pain has a negative impact on quality life of individuals, affecting sleep, nutrition, relationships, work capacity, functionality, and other aspects of daily life (SALVETTI et al., 2012).

In an attempt to justify this epidemic, about 35% of patients with chronic pain feel that your pain is not being well treated or controlled, pointing like main reasons the lack efficacy drugs that are prescribed and the lack attention, concern, importance and preparation of physicians in relation to pain patients (CASTRO-LOPES et al., 2010). Fleming et al. (2007) showed that 44% of chronic pain patients receiving opioid therapy (codeine, morphine, methadone) seek complementary and alternative forms of medicine. Among these alternatives, is herbal medicine. The problem is that patients do not always seek a correct and safe way to improve their treatment.

A product that has been gaining attention due its indiscriminate and exacerbated use is the Natural Life Harp (capsules 100 mg) that is presented as herbal medicine with numerous benefits including the solution "miracle" for chronic pain and numerous other indications such as: arthritis, bursitis, osteoarthritis, spinal disorders, rheumatic disorders, gout, herniated disc, varicose veins, asthma, cancer (breast, lung, brain, prostate), candidiasis, brain (prevents clots, stroke), cirrhosis, heart (prevent attacks, blood clots), diabetes, diarrhea, bone diseases, urinary diseases, premature aging, fever, gastritis, gastroduodenal ulcers, bleeding, herpes, menstrual irregularity, leukemia, blood pressure (reduced), reducing action mutagenic tobacco, calcification, chronic inflammation of various origins, (BRASIL, 2009).

It is important to mention that the product, Natural Harp, according to resolution number 5.684 of Health Surveillance Agency of Brazil (Anvisa) had their manufacture, distribution, trade and use prohibited on all national territory because it has no record, so there is no guarantee of quality, efficacy or safety of product.

Several versions of composition and how it is produced are found on internet. This product is sold clandestinely in several regions of Brazil and shopping sites, where it says that active component corresponds to *Uncaria tomentosa*, popularly known as "cat's claw".

Uncaria tomentosa is a species from Rubiaceae family, native throughout western Amazonia with potential as source of new drugs. Traditionally, the bark of cat's claw is prepared as a decoction, said to be beneficial in the treatment of many diseases such as: arthritis, bursitis, lupus and disorders of the stomach and intestines. Cat's claw bark contains oxindole alkaloids and polyphenols (flavonoids, proanthocyanidins, and tannins) and quinovic acid glycosides, pentacyclic alkaloids, and sterols. (SETTY, 2005).

This work aimed to make a case study through an analysis and discussion in legal and phytochemical fields of the product Natural Harp used for chronic pain.

MATERIAL AND METHODS

The product Natural Harp was acquired in market town of Belém, Pará, Brazil, without prescription. The product was marketed in plastic bottle with labeling indications and containing 15 capsules of 100 mg each.

2.1. Legal analysis, labeling and packaging

The legal aspect analysis of label and packaging was made in accordance with resolution (RDC) number 71 of 2009 (Anvisa). Furthermore, performed search product registration on Anvisa website, responsible for the control of medicines in Brazil.

2.2. Phytochemical analysis

For phytochemical analysis tests provided by Matos and co-workers in 1997, two product capsules were used. The powder obtained from

capsules was solubilized in 50 mL of hydro-alcoholic solution at 70% under mechanical stirring for 24 hours to form the test solution. A methanol extract of Uncaria tomentosa was used like standard solution.

2.3. Qualitative analysis of drugs

Samples of prednisolone, dexamethasone, hydrocortisone, caffeine, piroxicam, diclofenac sodium and dipyrone were diluted in hexane ethyl acetate solution (Hex:AcOEt), proportion 8:2 (v/v), were used for qualitative analysis of synthetic drugs. Then were applied to cromatoplacas silica gel and eluted with the mobile phase solution of dichloromethane and methanol in ratio 95:5 (v/v). For visualization in UV (254 nm) chamber was sprinkled ceric sulfate solution. All experimental procedure was performed in triplicate.

RESULTS AND DISCUSSION

3.1. Legal analysis, labeling and packaging

No registration at Anvisa and without minimum quality standards for packaging and labeling of products as defined in resolution number 71 of 2009 of Anvisa, as can be seen in Table 1 and Figure 1, the marketed product was considered illegal.

3.2. Phytochemical analysis

Reactions identification made during phytochemical screening showed the absence of compounds studied. On the other hand, Uncaria tomentosa (referred to as supposed product component) indicated presence of sterols, anthraquinones, tannins, flavonoids and polyphenols by means identification reactions. These results show that the product does not have as main composition the mentioned plant (table 2).

Table 2 - Phytochemical analysis

Compounds	Test (Natural Life Harp)	Standard (*Uncaria tomentosa*)
Saponins	-	-
Steroids	-	+
Anthraquinones	-	+
Flavonoids	-	+
Tannins and polyphenols	-	+
Carbohydrates	-	-
Alkaloids	-	-

Legend: (-) absence; (+) presence.

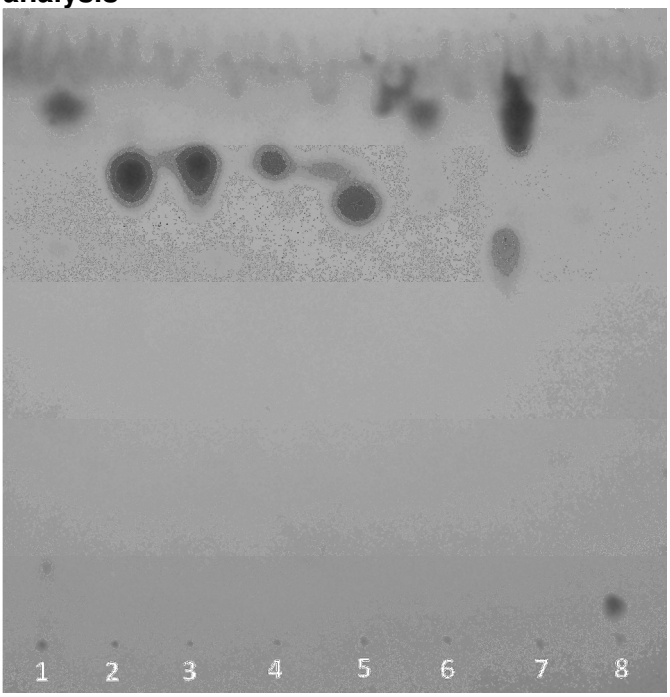
Figure 1 – Label product

Source: Authors.

3.3. Qualitative analysis of drugs

The thin layer chromatography (Figure 2) showed the presence of two non-steroidal anti-inflammatory drugs: piroxicam and diclofenac sodium, substances not indicated on the product label. This result (addition of drug isolated) mischaracterizes the classification of product as herbal medicine, because Anvisa sets herbal medicines like products obtained by employing exclusively derived from plant drug.

Figure 2 - Thin layer chromatography for drug analysis



Legend: 1 - Natural Life Harp; 2 - Prednisolone; 3 - Dexamethasone; 4 - Hydrocortisone; 5 - Caffeine; 6 - Piroxicam; 7 - Diclofenac sodium; 8 - Dipyrone.

Source: Authors.

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainly used in the treatment of inflammation, pain and edema, as well as in osteoarthritis, rheumatoid arthritis and skeletal

muscle disorders (BATLOUNI, 2010). 20% of patients cannot tolerate treatment with NSAIDs due effects occurring in gastrointestinal tract such as abdominal pain, heartburn and diarrhea (BHATT et al., 2008). The long-term treatment can cause erosions and gastric and duodenal ulcers . Although many patients do not have symptoms, are at high risk of developing serious complications, such as bleeding and perforation of the stomach. The annual risk of these serious complications is 1% to 4% in chronic treatment with NSAIDs (SCHEIMAN, 2010). Are more likely to present them elderly patients, women with rheumatoid arthritis, previous history of gastroduodenal bleeding in use of antithrombotic agents or corticosteroids, use of high doses of NSAIDs and the presence of severe systemic disease. Such side effects result from blockage of COX-1 in gastrointestinal mucosa and the consequent inhibition of prostacyclin production, PGE-2 and PGD-2 in the stomach (LANAS & SCHEIMAN, 2007). These prostaglandins serve as cytoprotective agents of gastrointestinal mucosa; inhibit acid secretion by stomach, increase local blood flow and secretion of cytoprotective mucus.

The spread of counterfeit drugs is a criminal activity that is increasing in many countries . Many of the existing fake products in the market have altered the composition in terms of quantities of active and inactive ingredients . According to the World Health Organization (WHO), counterfeit drugs are which is deliberately and fraudulently mislabeled with respect to identity and/or source. (SILVA, 2012).

The proliferation of industries without authorization and production of unregistered drugs brought the disadvantage of marketing products without supervision by health authority giving rise to several problems, including forgery . The counterfeit products have international dimensions, it has the need to promote cooperation among countries and regional cooperation to combat drug counterfeiting. Important factors that contribute to this practice include lack of adequate legislation, poor enforcement , weak penalties , situations of greater demand than supply and high prices (CARVALHO, 2005).

According to WHO (2005), there are two specific measures to combat counterfeiting of medicines, as the political will and the establishment of drug regulatory authorities. Political will refers to part of the responsibility that Government has in place initiatives to reduce counterfeit products and medication control to prevent this type of fraud to occur. Since the establishment of drug regulatory authorities, has a body responsible for investigating deviations of quality to ensure compliance with laws and regulations of medicines. Regular monitoring of establishments must be done so that they can be secured with Good Manufacturing Practices, and thus facilitate the tracking of medicines produced.

CONCLUSIONS

The searched product is outside of the legal requirements and addition of single drugs causes the product is not considered a herbal medicine.

The product proved to be adulterated with diclofenac sodium and piroxicam, bringing with it risk of intrinsic adverse events related to use of NSAIDs and corticosteroids. This events can be fatal depending on patient and clinical picture in question.

So, it is necessary a rigid inspection by health authorities, since this product was banned in 2009, but its market is found on the internet today.

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Table 1 - Analysis of product Natural Life Harp according to Anvisa resolution nº 71/2009.

ITEM Art. 5º	REQUIREMENTS	SITUATION	
		Presence	Absence
I	Trade name of the drug	X	
II	Generic name of each active ingredient, lowercase, using the Brazilian Common Denomination (DCB)		X
III	Concentration of each active ingredient per unit of measure or pharmacotechnique unit		X
IV	Route of administration		X
V	Total amount of net weight, volume and pharmaceutical units		X
VI	The total amount of feeders accessories accompanying the presentations, where applicable		X
VII	Pharmaceutical form	X	
VIII	Restriction of use by age group, the main face, including the phrase, in uppercase		X
IX	Qualitative and quantitative composition of each active ingredient, including, where applicable, salt equivalence basis		X
X	Preservation conditions, indicating the range of temperature and storage conditions, according to a study of drug stability	X	
XI	Name and address of the proprietor of the record in Brazil		X
XII	Name and address of the manufacturer, when it differs from the holder of the record company, citing the city and state, preceded by the phrase “Designed by:" and inserting the phrase "Recorded by:" before the data of the holder of the record company		X
XV	Number of National Register of Legal Entities (CNPJ) the registrant		X
XVI	Words "Brazilian Industry", when applicable		X
XVII	Name of the technician responsible, registration number and acronym of the company's Regional Pharmacy Council registrant's		X
XVIII	Phone Service Customer Service (SAC) of the proprietor of the registration or your responsibility		X
XIX	The abbreviation "MS" added the registration number in the ministry of health, requiring thirteen digits		X

Source: Authors.