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Identification of Undeclared Synthetic Drugs in Herbal Products Commercialized in Brazil: The "Indiano Talun" Case

Maria Izabel G. MORITZ [1], Karen L. LANG [1], Leopoldo BARATTO [1], Miguel S.B. CARO [2], Miriam FALKENBERG [1] & Eloir P. SCHENKEL [1]*

[1] *Departamento de Ciências Farmacêuticas y*
[2] *Departamento de Química, Universidade Federal de Santa Catarina, Campus Trindade 88040-970 Florianópolis, SC, Brazil*

SUMMARY. Capsules of a product called "Indiano Talun" are being commercialized in Brazil with the description: "C. Da Ídia Talun is a plant used to treat back pain, arthritis, osteoarthritis ...". The production and commercialization of "Indiano Talun" was forbidden by the Brazilian Agency of Health Vigilance (ANVISA) in June 2006. After some time, other products with similar packaging and labelling could be found in the market, as well as "Indiano Talun". The analysis of two samples "Indiano Talun" were completed. Sample A showed two main compounds, while Sample B had four. Both extracts were fractionated by column chromatography and one compound was isolated from each sample. UV, IR and NMR spectra were obtained and the structures could be esltablished as piroxicam for Sample A and ketorolac for Sample B. Comparative analyses by TLC and ^{1}H NMR of samples from the products "Chegou a solução Fator P" (2 samples from different sources) and "Fontes Life Fator P" (1 sample) showed them to be similar to Sample A containing piroxicam. In July 2007 "Indiano Talun" and "Fator P" were still being commercialized, mainly through Internet and also in other regions of the country. These results point to the urgent need for more intensive surveillance by health authorities and for a specific regulation concerning commerce of health products through Internet.

RESUMEN. "Identificación de Fármacos Sintéticos en "Productos Naturales" Comercializados en Brasil: el Caso Indiano Talun". "Indiano Talun" es un producto que estaba siendo comercializado en cápsulas, con la información en el rótulo de ser "una planta para el tratamiento de dolores en la columna, artritis, artrosis, bursitis y várices". Su producción y comercialización fueron prohibidas por la Agência Nacional de Vigilância Sanitária (ANVISA) en junio de 2006, pero tiempo después podía ser encontrado con otra presentación, con embalajes y finalidad medicinal semejante, pero nombres diferentes. Se analizaron dos muestras de lotes diferentes de "Indiano Talun". La Muestra A mostró dos components mayoritarios y la Muestra B, cuatro. Las dos muestras fueron fraccionadas por cromatografía en columna, aislándose una substancia mayoritaria de cada muestra. Estas substancias fueron caracterizadas por métodos espectrocópicos (UV, IR y RMN) como piroxicam (Muestra A) y ketorolac (Muestra B). Tres muestras de productos análogos, comercializados con otros nombres ("Fator P" e "Fontes Life") también fueron investigados por cromatografia en capa fina y ^{1}H RMN, comprobándose la presencia de piroxicam en todas ellas. Estos productos similares a una de las muestras de "Indiano Talun" continuaban siendo comercializados en varias regiones de Brasil hasta julio de 2007, especialmente a través de Internet. Estos hallazgos confirman la necesidad urgente de una fiscalización más intensa por parte de las autoridades sanitarias, así como la reglamentación específica del comercio por Internet de productos relacionados con la salud.

INTRODUCTION

Herbal medicines are increasingly popular in many countries, based on the putative absence of adverse reactions. From time to time, there are reports in the literature from different countries concerning the adulteration of such "natural products" with synthetic drugs [1]. Such occurrence was yet not described in South America. We report the analysis of five products commercialised in Brazil, outside the pharmacy distribution chain, mainly in natural products stores, by Internet sites and also by door-to-door vendors. These products have similar packages and declarations, notwithstanding their different names.

The first product we analysed was a sample of "Indiano Talun" provided by a physician (sample A), who reported of patients describing the product as very powerful and fast in alleviating pain. The second product (sample B) presented also the name "Indiano Talun", but had a different presentation from sample A and was supplied by the Toxicological Information Cen-

KEY WORDS: Adulteration, Herbal products, Indiano Talun, Ketorolac, Piroxicam.
PALABRAS CLAVE: Adulteración, Herboristería, Indiano Talun, Ketorolac, Piroxicam.

* Author to whom correspondence should be addressed.. *E-mail:* schenkel@ccs.ufsc.br

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ter of the Federal University of Santa Catarina (CIT/UFSC), Florianopolis, which received it from the municipal health vigilance service.

The production and commercialization of "Indiano Talun" was forbidden by the Brazilian Agency of Health Vigilance (ANVISA) in June 2006 [2], but after a period the product could be found with a different presentation (Fig. 1), together with other products described as "Fator P" (in two different forms: "Chegou a solução - Fator P" and "Fontes Life - Fator P"), with similar packaging and labelling. The analysis of two samples of "Indiano Talun" (A and B) and three samples of "Fator P" was performed by chromatographic and spectroscopic methods.

Figure 1. Frontal view of the analysed samples, named "Indiano Talun", "Chegou a solução - Fator P" and "Fontes Life - Fator P" (from left to right).

MATERIALS AND METHODS

All analysed samples consisted of plastic bottles containing capsules (Fig. 1) and were provided by different sources, as described in Table 1. Two samples declared the producer laboratory in the label of the product ("Ervas Natu's") but none included the address or register other data.

Extraction

The content of capsules of each product (the number varied according with the availability), was extracted with methanol for 15 minutes, using an ultrasound bath. The extract was filtered.

Thin Layer Chromatography

The extracts were analysed on silica gel F254 plates, using dichloromethane / methanol (9:1) or ethyl acetate: methanol (7:3), as eluent. Analgesic and/or anti-inflammatory drugs (pharmaceutical grade) were used as comparison substances. Plates were observed under UV 254 and 366 nm, sprayed with Ehrlich reagent or sulfuric anisaldehyde and heated to enhance reaction. The extracts of samples analysed earlier and the compounds isolated from these products were applied as standards for the analysis of later samples.

Isolation of compounds

Sample	Product Name according to label (Characteristics of package)	Supplier (Local, Period)	Additional Information in the Label
A	"Indiano talun - C. da India Talun" (White flask, with label pressed in green color directly on the plastic flask)	Physician whose patients were using it (Florianopolis, SC, May 2006)	"É uma planta usada para combater dor de coluna, artrite, artrose, bursite e varizes. Produto isento de registro Dec. 79994/77 Art. 28 e 29 Lei 7.370"
B	"Indiano Talun - C. Da India Talun" (White flask, green label with yellow or black inscriptions)	Toxicological Information Center, Federal University of Santa Catarina (CIT/UFSC), (Florianopolis, SC, June 2006)	"É uma planta usada para combater dor de coluna, artrite, artrose, bursite e varizes. Produto isento de registro Dec. 79994/77 Art. 28 e 29 Lei 7.370"
C	"Chegou a solução - Fator P" (White flask, yellow label with blue or black inscriptions)	A consumer (Brusque, SC, November 2006)	"É uma planta usada para combater dor de coluna, artrite, artrose, bursite e varizes."
D	"Chegou a solução - Fator P 100 mg" (White flask, green label with yellow or black inscriptions)	Ezequiel Dias Foundation (FUNED), (Belo Horizonte, MG, December 2006)	"É uma planta usada para combater dor de coluna, artrite, artrose, bursite e varizes."
E	"Fontes Life - Fator P 100 mg" White flask, green label with yellow or black inscriptions)	A consumer (Marau, RS, June 2007)	"É uma planta usada para combater dor de coluna, artrite, artrose, bursite e varizes."

Table 1. Analysed samples and their characteristics, concerning name of the products, source and information in the label.

As the capsules from Samples A and B were available in large amounts, the isolation procedures were performed with them. The content of 15 capsules from each sample was extracted three times with methanol for 15 min in an ultrasound bath, and the filtered extract was concentrated to dry extract under low pressure. Both extracts were fractionated on silica gel columns. Extract A was submitted to vacuum liquid chromatography with a dichloromethane / methanol gradient. Extract B was by partitioned with growing polarity solvents (petroleum ether, methylene chloride and methanol), and after this the methanol fraction was fractionated in a column with ethyl acetate / methanol (70:30). The fractions with the main compounds were pooled and further chromatographic columns were performed until pure substances were obtained.

Spectral analysis

Ultraviolet (UV), Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectra were obtained for the compounds isolated from Samples A and B, as well as for the totlal extracts of samples C, D and E. UV spectra were measured in methanol in a Lambda 10 UV/Vis Spectrometer (Perkin Elmer). IR spectra were recorded in KBr disk in a IR Prestige-21 FTIR-8400 S (Shimadzu). NMR spectra were performed in $CDCl_3$, in a Bruker AM 500 (500 and 125 MHz) or a Varian AS-400 NMR spectrometer (400 and 100 MHz).

RESULTS

An initial analysis of the extracts from Samples A (920 mg) and B (1.0 g) gave no evidence of plant metabolites such as chlorophyll, flavonoids or terpenoids. Instead, we observed the presence of few substances, detected by fluorescence quenching, some of them with a positive reaction to Ehrlich reagent (Fig. 2), suggesting the presence of synthetic drugs. Based on the reported immediate effect *in alleviating pain,* extract A was analysed by chromatography using as references some widely used analgesics and nonsteroidal anti-inflammatory drugs - NSAIDs (Fig. 3). The chromatographic analyses pointed to different compositions. Sample A presented two main compounds, and sample B, four. None could be identified at this first stage. Due to this both extracts were fractionated by column chromatography and from each run one main compound was isolated, named Compounds **1** and **2**.

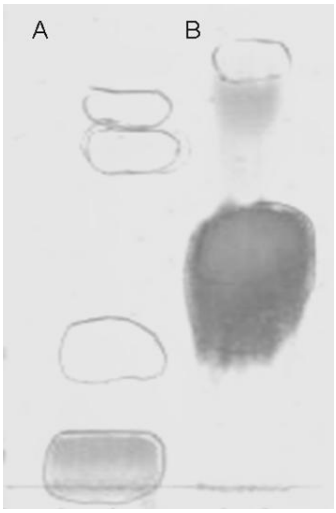

Figure 2. Thin layer chromatography of methanolic extracts from samples **A** (Fator P) and **B** (Indiano Talun). (Silica gel, EtOAc: MeOH 7:3 v/v. Detection with Ehrlich Reagent.

Compound 1 was obtained as a white powder, melting point 214 °C. The IR spectrum displayed strong signals at 1529 and 1348 cm^{-1} and further characteristic signals for hydroxyl (3350-3500 cm^{-1}; 1174 cm^{-1}) and carbonyl groups (1745 and 1628 cm^{-1}). The UV spectrum displayed three absorptions at λmax. 358, 289 and 256 nm, suggesting a highly conjugated system [3,4]. The ^1H NMR spectrum displayed signals mainly in the aromatic region, with the exception of a singlet for a methyl group at δ^1H 2.95, And two other large signals δ^1H 8.89 and *ca.* δ^1H 13.29, possibly related to amide and hydroxyl hydrogen atoms. Detailed analysis of the COSY spectrum pointed to the presence of two spin systems (each with four hydrogen atoms), the first one being 8.07 d J = 8.4; 7.77 m; 7.92 dd and 7.77 m, the second was 8.25 d; 7,77 m;

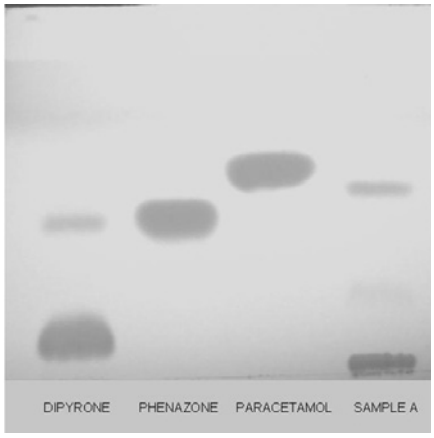

Figure 3. Thin layer chromatography of methanolic extract from sample A (Indiano Talun) compared with some analgesic drugs. (Silica gel, CH_2Cl_2 : MeOH 9:1 v/v , UV 254 nm).

7.13 dd; 8.37 d. The ^{13}C NMR spectrum showed 15 signals for carbon atoms, most of them in the aromatic region, with the exception of a signal for a methyl group at $\delta^{13}C$ 40.0, and two further signals displaced downfield at $\delta^{13}C$ 158.7 and $\delta^{13}C$ 166.9. These were not connected to hydrogen atoms, as indicated by the HSQC spectrum. Detailed analysis of the COSY, HSQC and HMBC spectra allowed to establish unambiguously the connectivity and revealed the substance as the known anti-inflammatory drug *piroxicam* (Fig 4a).

Compound 2 was obtained as a white powder, melting point 146-153 °C. In the IR spectrum it displayed characteristic signals for carbonyl groups (1720 and 1612 cm^{-1}). The UV spectrum displayed two absorptions at λmax. 324 and 226 nm, suggesting a highly conjugated system [3,4]. The ^{1}H NMR and COSY spectra pointed to the presence of three spin systems. One in the aromatic region with five hydrogen atoms (multiplets between $\delta^{1}H$ 7.5 and $\delta^{1}H$ 7.8), the second constituted by a coupled pair of doublets ($\delta^{1}H$ 6.82 and $\delta^{1}H$ 6.14, J = 3.2), and the third system formed by multiplets and a triplet (4.48 m; 4.38 m; 2.83 m and 4.09 t). The ^{13}C NMR spectrum showed 15 signals, and the DEPT spectrum revealed two methylene and one methyne carbon in the aliphatic region and five quaternary carbon atoms, two of them without connectivity to hydrogen atoms and assignable to carbonyl groups, at $\delta^{13}C$ 185.8 and 174.1 [3,4] (Table 2). Detailed analysis of the COSY, HSQC and HMBC spectra allowed to establish the connectivity and revealed the substance as the known anti-inflammatory drug *ketorolac* (Fig. 4b).

NMR data, UV and IR spectra are coherent with the literature [5-7]. The NMR data for these compounds is not commonly found in literature, and considering that these compounds can be detected by the NMR spectra of the products, they are presented in the Table 2.

DISCUSSION

The Brazilian Agency of Health Vigilance (ANVISA) has forbidden the production, distribution, commercialization and utilization of the product "Indiano Talum 100MG - C. Da Índia Talun" by the Resolution RE1864, of June 14th 2006, as the laboratory was not registered by ANVISA or allowed to operate [2]. After identifying ketorolac and piroxicam in the samples, one of the authors sent ANVISA a communication of the results and informed that the product was still being commercialized. In November 2006,

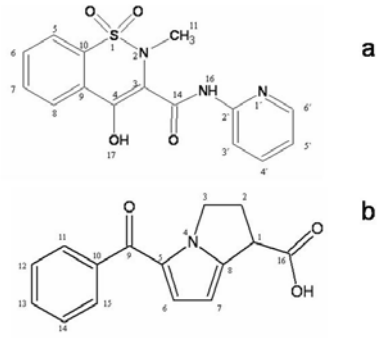

Figure 4. Structures of compound **1**, identified as piroxicam (**4a**) and compound **2**, identified as ketorolac (**4b**).

ANVISA determined the apprehension of "Indiano Talun" in whole Brazil [8], and in February 2007 another Resolution extended the apprehension to "Fator P" [9]. In July 2007, an integrated operation of Federal Police and ANVISA called "Operação Placebo" was carried out, leading to the apprehension of illegal "Herbal products", labels and empty packages in many Brazilian states [10]. After that operation, we performed an Internet search through Google, searching for "Indiano Talun" or "Fator P", and in contrast to searches completed months before, practically nothing was found. Despite this, searching for "Fontes Life" in the same site [11], two discussion forums about the product "Fator P" were found, where exchange of messages of users and handlers could be read after Operation Placebo, as well as a blog where a handler announced "Fontes Life" in the same way as "Indiano Talun" was previously announced, as being "a plant....". Many users in the forums have mentioned the same handler [12,13].

Besides advertisements of the product (delivery by express post "Sedex"), people asked in these discussion forums on "how to get the product?", about its composition, origin, side effects, counterindications and price. Some users expressed strong feelings concerning the lack of reliable information and the contradictions in the data circulating on the Internet [12,13], since the product was sold as a bottle without package inserts. In this case, the only information available for patients was represented by the label and there was no information concerning the composition or advise to potential users. Clearly, the utilization of pharmaceuticals without identification on the labels can lead to adverse reactions and interactions with other drugs that patients are using, mainly in those drugs with narrow therapeutic indexes.

In the case reported, potent analgesic and

1 piroxicam			**2** ketorolac		
Atom	**δC**	**δH mult., *J* Hz**	**Atom**	**δC**	**δH mult., *J* Hz**
1		-	1	42.8	4.09 t
2	-	-	2	31.1	2.83 m
3	111.6	-	3	47.7	4.38 m; 4.48 m
4	158.7	-	4	-	-
5	124.9	7.92 dd, J 7.2	5	126.8	-
6	133.1	7.77 m	6	126.1	6.82 d, J 3.2
7	132.6	7.77 m	7	103,4	6,14 d, J 3.2
8	126.7	8.07 dd, J 8.4	8	144,9	-
9	128.4	-	9	185,8	-
10	134.6	-	10	139,2	-
11	40.0	2.96 s	11	128,7	7.75 d, J 7.6
12			12	128.2	7.49 t, J 7.6
13			13	131,6	7,56 t, J 7.2
14	166.9	-	14	128.2	7.49 t, J 7.6
15	-	-	15	128.7	7.75 d, J 7.6
16	-	8,89 s	16	174,1	-
17	-	13,29 s			
2´	150.2	-			
3´	114.3	8.25 d, J 8.4			
4´	138.5	7.77 m			
5´	120.6	7.13 dd			
6´	148.3	8.37 d, J 4.5			

Table 2. NMR data of compounds **1** (piroxicam) and **2** (ketorolac).

anti-inflammatory drugs, that should be used only as prescription medicines, were found. Possibly many patients were taking the product without knowledge of their physicians. Even if the professionals were told, they could not have idea on the composition and the risk their patients were going into, so patients could be taking potent drugs without the professional follow-up that such drugs require.

Ketorolac is a potent analgesic, with moderate anti-inflammatory effect. Since it is one of the few NSAIDs approved for parenteral administration, it should not be used for routine analgesia [14]. Opinions on its safety are conflicting. Anyway, the risk of adverse effects is considered higher when ketorolac is used for more than five days or in elderly [15]. Effects on the central nervous system (somnolence, headache, dizziness), as well as gastrointestinal effects (nausea, dyspepsia, abdominal pain) are most commonly reported, but edema, hyperkalemia and impaired renal function have also been reported. A case-control study on hospitalization for gastrointestinal bleeding or perforation showed ketorolac to be more gastrotoxic than all other NSAIDs, but the relative risk is higher for intramuscular than with oral administration [15].

Due to a very long half-life (40 to 100 h), piroxicam can accumulate [16] and lead to gastrointestinal (up to 40% of patients) and nervous system (about 11%) adverse effects. This drug should be avoided in cases of renal insufficiency and in the case of long-term therapy, the renal function should be monitored [15].

Both drugs are highly bound to plasma proteins (99%) and may displace other drugs. These interactions can be especially problematic with warfarin, hypoglycemic sulfonylureas and methotrexate [14]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also attenuate the effect of ACE inhibitors, and the combination of these compounds with NSAIDs can produce bradycardia and lead to syncope, mainly in patients with hypertension, diabetes, ischemic heart disease and in the elderly [14]. Piroxicam and ketorolac can reduce the renal excretion of lithium, so caution should be taken with patients taking these drugs [14,15]. The risks of taking ketorolac or piroxicam should be in the recommended indications in the label of the products, and will depend on the condition of each patient, but no reasonable benefit should be expected as the quality of the products is not assured.

"Miracle drugs" can be especially attractive to people with chronic diseases that still do not have a really successful treatment and so demand a palliative approach. Even in the present time, with so much available information in different media, the overwhelming amount of bad quality information on health issues can lead

people to pay a lot for products that are not safe, not effective or even not legal in the market. In the case reported, with the demonstratedadulteration of a product declared as a plant drug with potent synthetic drugs, there is a clear exploitation of the popular belief "if it is natural, it can't hurt". In our opinion, the promotion of herbal medicines as natural safe alternatives, neglecting the possibility of adverse reactions and drug interactions, contributes to the utilization of unsafe and unregulated products. Presently, such kind of illegal products can have a greater damage potential considering the easy and fast spread of information through Internet, sometimes having propaganda presented as health information. In this context, consumers should be aware about the risks of taking any product that does not follow the sanitary legislation of each country, and should also receive clear information on how to identify adulterated or illegal pharmaceutical products.

CONCLUSIONS

The case of "Indiano Talun"/"Fator P"/ "Fontes Life" reported here points to the urgent need for consumer education and for more intensive surveillance by health authorities concerning adulterated or illegal pharmaceutical products. In this context, the role of all health professionals needs to be emphasized, particularly that of pharmacists in their position as the health professional that can be contacted most easily by patients. The case also points to the need for specific regulations relative to the commerce of health products in the Internet. Without specific regulations, the Internet commercialization of medicines and dietary supplements, particularly without a good surveillance system, will leave public health in danger.

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