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Research Paper

Folk pharmaceutical formulations in western Mediterranean: Identification and safety of clays used in pelotherapy

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ABSTRACT

Ethnopharmacological relevance: Clays are naturally occurring ingredients of many natural health products, being included in most of ancient Mediterranean/European medical texts and currently used to prepare therapeutic hot-muds (peloids) in several thermal stations of the Mediterranean region. Clays are included in the formulation of peloids as vehicles of the mineral-medicinal water, to obtain inorganic gels with rheological and thermal properties suitable to be topically applied. Knowledge about formulations and preparation procedures of these traditional medicines has been orally transmitted since ancient times. Increasing recognition of the therapeutic utility of these traditional and natural health care substances make necessary a full ethnopharmaceutic research to ascertain those compositional characters that allow to establish quality attributes and corresponding requirements for these materials and products, including identity, purity, richness and safety.

Materials and methods: Five clay samples (A, B, C, D and E) currently used in various spa centers of southern European/Mediterranean countries were studied. X-Ray diffraction (XRD) and X-ray fluorescence (XRF) data were used to asses sample identity and richness. Elemental impurities and microbiological contaminants were also determined and compared to normative limits. Particle size distribution was related to their safety as powder materials.

Results: Samples A, C, D and E were identified as "high purity clay", while sample B was identified as a mix of clay minerals and carbonates. The presence of carbonates in this sample could compromise its suitability for pelotherapy. The studied clays meet the main normative limits for metals impurities, with the exception of arsenic in sample A and nickel in sample B. The samples comply with the microbiological limits proposed by European legislation for medicinal products. According to the particle size of the studied samples, prevention and control of dust exposure must be considered.

Conclusions: Despite their demonstrated longevity, the use of clays in traditional medicine formulations as peloids greatly requires comprehension of their identity and safety attributes. Continuity of these mineral substances as recognized health care ingredients oblige to conduct interdisciplinary research to know the features that sustain their traditional use in the preparation of medicines (ethnopharmaceutics).

1. Introduction

Traditional medicine involves the use of naturally occurring materials, mainly plants and plant parts, but also inorganic materials, and in particular, clays. On behalf of their healing properties, clays had been included in most of ancient Mediterranean/European medical texts (De Vos, 2010), being used to treat skin pathologies (antiseptic cataplasms), intestinal and stomach diseases (because of its astringent and adsorbent properties) as well as in balneotherapy (Carretero et al., 2006).

Nowadays, modern medical care continues to use clays as highly significant health care ingredients in industrial products (López Galindo and Viseras, 2004) as well as in natural remedies and dietary supplements (http://www.dsld.nlm.nih.gov/dsld/). In western medicine, clays are used in patent medicinal products both as pharmacologically inactive ingredients (abrasives, adsorbents, anticaking agents, glidants, coating agents, opacifying agents, viscosity-increasing agents, emulsion stabilizers, binders or suspending agents) (Viseras et al., 2007; Rowe et al., 2009), and as pharmacologically active substances for the prevention, relief or cure of skin pathologies, inflammations, contusions, and

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gastrointestinal disorders (López-Galindo et al., 2011; Carretero et al., 2013).

In the last century, the use of clays in traditional European medicine had been practically limited to medical hidrology (pelotherapy), with only some exceptions in folk European (Pieroni et al., 2004) or migrant communities pharmacopoeias (Ellena et al., 2012). Despites the longevity of clays as therapeutic ingredients ("Terra sigillata" was probably the first patented medicine (Finkelman, 2006)), the dominant European health care system, based on allopathic medicine, considers the use of clays in traditional medicine as "complementary", "alternative" or "non-conventional" remedies. However, traditional medicine in developed countries is gaining popularity because it offers less adverse effects and gentler means of managing chronic diseases (heart disorders, cancer, diabetes…) in comparison with allopathic medicine (WHO, 2005). In particular, several studies have analyzed the effectiveness of pelotherapy in patients with rheumatic diseases versus allopathic therapies, noticing improvements in quality of life or drug consumption (Bostan et al., 2010; Fioravanti et al., 2012; Espejo Antúnez et al., 2013). Pelotherapy involves the topical application of heated muds, constituted by semisolid dispersions of clayey solid phases into mineral-medicinal waters (Veniale et al., 2004). The selection of mud components, as well as their preparation and application procedures follows traditional knowledge; the systems are frequently prepared and used without proper understanding of their composition and quality controls. However, confirmation (or refutation) of the possible effectiveness of these natural health care products would absolutely require a scientific orientation focused to assure applicable requirements (López-Galindo et al., 2007). It is desirable to design and implement quality systems involving adequate control of raw materials, procedures and final products.

Clays are included in the formulation of peloids as vehicles of the mineral-medicinal water, to obtain inorganic gels with rheological and thermal properties suitable to be topically applied. Knowledge about formulations and preparation procedures of these traditional medicines has been orally transmitted since ancient times. The study of these folk medicinal products involving identification of the ingredients and preparation procedures fall into the concept of ethnopharmaceutics, as a part of ethnopharmacy (Heinrich and Pieroni, 2001).

With these premises, this study is a first step in a much larger project aimed to address the traditional therapeutic use of clays in European/Mediterranean countries in view of establishing the minimum compositional requirements that should be comply to make possible the evaluation of clinical efficacy of the treatments based on these natural inorganic substances. For these purposes, and following pharmacopoeias and international guidelines (www.healthcanada.gc.ca/nhp; ICH, 2013), this study aims to determine compositional attributes of clay samples used in European/Mediterranean thermal stations, including identity, purity, richness and safety of these natural ingredients.

2. Materials and methods

Five clay samples (A, B, C, D and E) used to prepare peloids in 17 spa centers of three southern European/Mediterranean countries (Italy, Spain and Tunisia) were studied. Sample A was Volcangel© gifted by BENESA (Spain). Sample B was gifted under confidential agreement. Sample C was Peloide Minerale® from SO.MI.ES. (Italy). Sample D, came from Jebel Aidoudi deposits (Tunisia) and sample E was Innogel LBB® clay purchased from Aplicaciones especiales del Vallés S.L. (Spain). Selected samples were representative of the raw materials used by a large number of thermal spas. All samples were milled, sieved ($< 125\ \mu m$) and dried in oven (40 °C) before carrying out any test.

2.1. Identity and richness

X-Ray diffraction (XRD) data and chemical analysis (major elements) were used to asses sample identity and richness. The mineral quantification was based on the measurements of peak areas in the diffractograms according to Biscaye (1965) and Moore and Reynolds (1989), and corrected with chemical data (López-Galindo et al., 1996) using the XPOWER® program (http://www.xpowder.com/) (Martín-Ramos, 2004). XRD analysis was done by using a Philips® X-Pert (Philips, Holanda) diffractometer equipped with automatic slit (CuKα, 4–70° 2θ, 6°/min, 40 kV) both on bulk random and oriented aggregated samples (glycolated and heated to 550 °C). Major elements were determined by X-ray fluorescence (XRF), using a Bruker® S4 Pioneer equipment, with a Rh X-ray tube (60 kV, 150 mA).

2.2. Purity

2.2.1. Trace elements

The following elements were analyzed by an ICP/MS Perkin-Elmer® SCIEX Elan-5000 equipment prior sample digestion with "aqua regia" (HNO_3+3HCl): Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Mo, Ni, Pb, Sb, Se and Tl. Accuracy was in 1–3% range, depending on the element amount. The analyses were carried out by Activation Laboratories Ltd. (Canada).

2.2.2. Microbiological contaminants

Microbiological test were carried out according to European Pharmacopoeia methods (EP 7.0., 2011). The analysis included total viable aerobic, contaminating fungi (yeast and mold), *Salmonella spp., Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa*.

2.3. Particle size distribution

Particle size analysis was performed with a Malvern® Mastersizer 2000 LF granulometer. Prior to the analysis, a few milligrams of powder sample were dispersed in purified water and sonified for several minutes.

3. Results and discussion

3.1. Identity and richness

Mineralogical compositions of the samples (Table 1) were determined on the basis of XRPD patterns (Fig. 1) and chemical compositions (Table 2). Samples A, C, D and E were identified as "high purity clays" as the sum of minerals assigned to this group (smectites, kaolinite, illite and chlorite) was > 70% w/w. Sample B was identified as a mix of clay minerals (illite, chlorite and kaolinite) and carbonates (calcite and dolomite). Significant presence of carbonates (13% w/w) was also detected in sample C. Several authors have pointed out the importance of the presence of high content of clay minerals (in particular smectites) in samples to be used in pelotherapy, because rheological, thermal and chemical features associated to these minerals improve some performances (Veniale et al., 2004; Carretero et al., 2007; Rebelo et al., 2011). Carbonates can be considered as "inert" impurities, even if their high relative amount in sample B could compromise its suitability for pelotherapy. Crystalline silica (quartz) was also measured in all the studied samples. This mineral is usually present in all clay deposits, but its occurrence in health care