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BENEFITS AND RISKS OF CLAYS AND CLAY MINERALS TO HUMAN HEALTH FROM ANCESTRAL TO CURRENT TIMES: A SYNOPTIC OVERVIEW

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Abstract—Clay, or more precisely, certain clay typologies, have been used traditionally by humans for therapeutic, nutritional, and skin-care purposes though they may be responsible for some relatively rare but significant health and skin-care risks. For example, clay particles could adsorb and make available for elimination or excretion any potential toxic elements or toxins being ingested or produced, but they could also adsorb and make available for incorporation, through ingestion or through dermal absorption, toxic elements, e.g. heavy metals. Geophagy has been observed in all parts of the world since Antiquity, reflecting cultural practices, religious beliefs, and physiological needs, be they nutritional (dietary supplementation) or as a remedy for disease. Some clays and clay minerals are employed widely in both the pharmaceutical and cosmetics industries as active compounds/agents and as excipients. In the biomedical field, some clay minerals such as halloysite and montmorillonite are known for their effective role as carriers for the control and sustainable delivery of active drug molecules, and in the biomaterials field some clay minerals are used for scaffold, hydrogel, foam, and film production. Constraints, both chemical and microbiological, on the use of clay-based products for therapeutic and cosmetic topical applications are generally imposed by sanitary regulations, and some solutions are proposed herein to control and reduce such restrictions. Particular emphasis is placed here on peloids and pelotherapy, as well as on manipulated and modified peloids, and specifically on tailored peloids or 'designed and engineered' peloids, and their derivatives, bactericidal peloids and ointments. As far as the so-called 'killer clays' are concerned, their pre-requisites, mechanisms of action, and disinfection role are also enhanced. Podoconiosis is an environment-related or geochemical disease that occurs in tropical highland areas, and is caused by long-term exposure of bare feet to volcanic, red-clay soil and affects some people, particularly those working in agriculture in some regions of Africa, Asia, and South America.

Keywords—Clay–human health interactions · Geophagy · Killer clays · Peloids and pelotherapy · Pharmaceuticals and cosmetics · Podoconiosis

INTRODUCTION

The historical evolution of the use of minerals (including clays and clay minerals) for human healthcare is probably as old as the human species itself. It was first applied on an empirical basis, and later moved to a scientific basis initiated at the dawn of the scientific revolution, in the Renaissance, and continued to modern and current times, acknowledging the important roles of the so-called 'healing clays' and certain clay minerals for therapeutic, nutritional, and skin-care uses. Such evolution, particularly in terms of the clays involved, can be found in publications such as those by Duffin et al. (2013) and Gomes and Rautureau (2021a).

Clay has been used by humans, for healing purposes, for longer than most other earth materials, starting during Antiquity particularly in Mesopotamia by Sumerian, Assyrian, and Babylonian cultures. The ancestral and earliest references to the use of clay in the form of mud for the treatment of gynecological disorders and infections are found in the Lahun papyrus dated from the19th century BCE, and only discovered in 1889. The famous Nippur plates or tablets (~2500 BCE), found in Mesopotamia, and the Ebers papyrus (~1500 BCE) from Ancient Egypt, describe the treatments (method and dose) of some diseases using drugs based on 500 substances, including clay and other minerals, especially copper, lead, and antimony minerals. It was in Ancient Greece that the famous clay-based medicinal earth or *sigillata terra* was discovered, and exploited in certain volcanic islands of the Aegean Sea. Medicinal earths, which are known to be composed of clay, were commercialized and were used since Antiquity up to the 18th century (Bech, 1996, 2010; Duffin et al., 2013; Macgregor, 2013; Hall & Photos-Jones, 2008; Photos-Jones & Hall, 2011; Photos-Jones et al., 2015, 2017; Retsas, 2012, 2016). Each of those islands produced its own medicinal earth, named after its geographic origin, the most famous being the Lemnian earth from the Lemnos Island, which was first used around 500 BCE as an antidote for snake bites, as an antidote to any poison taken orally, and to cure ulcers and dysentery. The torches (small disks) of sigillata earth were crushed into powders and taken with liquids or made into pastes and smeared on painful parts of the body. The increasing worldwide demand for medicinal earths inspired many counterfeits and imitations; the increasing need led to the survey of sources of similar medicines which were found, particularly during Medieval and post-Medieval times, and were prepared and commercialized in Hungary, France, Germany, Malta, and Silesia (Poland).

Clay uses continued through the Roman and Byzantine-Ottoman civilizations. In Medieval times, the Arab doctors

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Avicenna (980–1037), in his book *El Canon*, and Averroes (1126–1198) encouraged the use of medicinal mud and classified various types of mud. The Arab doctor Ibn al-Baitar (1197–1248) was the author of a book of pharmacology that mentions eight types of clay-based medicinal earths for therapeutic and cosmetic uses (Duffin et al., 2013; Gomes & Rautureau, 2021a).

During the Renaissance when the first texts of the so-called Pharmacopoeias, namely the *Pharmacopoeia of Valence*(1601) and the *Pharmacopoeia Londinensis* (1618), were published, their texts mention various drugs, some based on minerals, and how to use them to treat a number of topical and internal symptoms or diseases.

The First Industrial Revolution began in Great Britain in the 1760s. This was when the abundance of metal ores (iron, tin, and copper), coal, clay (China clay or kaolin, ball clay, fullers' earth, and fire clay), and water (high-quality resources and reserves) associated with great education reforms were the driving agents of the significant advances verified in both science and technology, particularly in chemistry and pharmacy. Manual production methods gave way to methods using machines.

Chemistry and pharmacy had the benefit of significant developments identified as 'New Chemistry' or 'Chemistry Revolution' and 'New Pharmacy' or 'Pharmaceutical Revolution' associated with the French Revolution and pioneered by Antoine-Laurent Lavoisier (1743–1794) and by Antoine-François Fourcroy (1755–1809), respectively. The concept of Public Health, and the interest in public hygiene and in the control of health threats resulting from rapid industrialization and urbanization, as well as from geological influences on health, only appeared in the late 18th and 19th centuries. During the 20th century, clay/mineral water mixtures with various solids contents were used widely in Europe, particularly in France, Germany, Italy, and Spain, for topical therapeutic applications, in the form of mud-baths and poultices.

Compared to other natural materials used for human health care, clays and clay minerals have the characteristic of being able to penetrate the various natural barriers of the human body through the following pathways: ingestion, inhalation, and skin absorption.

Geophagy, defined as the intentional consumption of earth, particularly clayey soil and clay (Abrahams 2002, 2005, 2012, 2013; Kmiec et al., 2017; Seim et al., 2013, 2016; Wilson, 2003; Young 2010; Young & Miller 2019; Young et al., 2008), has long been practiced by humans of various geographies. Despite numerous studies, the causes and consequences of geophagy (benefits and hazards) remain inadequately identified and understood, a situation equally applicable to the varieties of geophagy known as bucarophagy and pucarophagy, which were practiced in Spain and Portugal, respectively, at various times.

Recent research has reinforced the potential of clays and clay-mineral applications in the pharmaceutical, biomedical, and cosmetics fields. Among all clay mineral species, those used most for pharmacological applications are kaolinite, halloysite, montmorillonite, talc, palygorskite, and sepiolite. Some can be included in formulations to be used, for example, as antacids to reduce gastric acidity, as gastrointestinal protectors, and as antidiarrheals. Others are used extensively as excipients in some formulations, acting as diluents, binders, emulsifiers, and carriers of biologically active molecules for improving the physiological availability of drugs (Carretero, 2002; Carretero & Pozo, 2009, 2010; Carretero et al., 2006, 2013; Gomes, 2013; Gomes & Silva, 2007; Gomes et al., 2021b; Kim et al., 2016; López-Galindo & Viseras, 2004; Massaro et al., 2018).

Some natural clays as well as some which are artificially manipulated, maturated, and modified in the form of mud-bath, mud pack, and compress have been used outdoors (in natural sites) or indoors in spa facilities as healing materials: the so-called natural peloids and peloids *stricto sensu* (Carretero 2020a, 2020b; Gomes et al., 2013, 2021a). Some natural clays and some manipulated and modified clays can exhibit bacteriostatic and bactericidal properties which can be used, e.g., to develop bactericidal peloids and bactericidal ointments (Gomes et al., 2020, 2021a). When clay is applied topically in the form of healing mud and peloid, or when clay participates in cosmetic formulations, persistent skin absorption of potentially toxic elements and compounds may cause exposure to toxicity.

Although rare, situations arise in which clay can harm human health, particularly if the clay particles are inhaled persistently, causing respiratory diseases; ingested persistently (geophagy of clayey soil and edible clay); or absorbed dermally (podoconiosis), causing diseases the severity of which depends on exposure´s dose and duration.

Podoconiosis affects agricultural workers who work in their bare feet in some regions of sub-Saharan Africa, Asia, and South America (Chandler et al., 2021; Davey et al., 2007; Deribe, 2017; Deribe et al., 2015a, 2015b, 2015c, 2018; Feleke, 2017; Gomes et al., 2021a; Lyles, 2018).

The present article is not a 'standard review' *per se*, because the intention is to provide pertinent information (including novel results produced by the authors) on both the benefits and hazards of interactions between clays and clay minerals and human health. These interactions include geophagy, therapeutics and cosmetics, peloids and pelotherapy, and diseases such as podoconiosis (a tropical/subtropical disease the etiology of which has been attributed to clays and clay minerals from red soils rich in iron (oxyhydr)oxides, and which can cause significant physical disability and psychological comorbidity).

SPECIFIC PROPERTIES OF CLAYS AND CLAY MINERALS THAT COULD JUSTIFY ONGOING HEALTH USES AND FUNCTIONS

The definition of clay is still not unanimous, even among people who study and use clay for various scientific and technological purposes. In fact, the numerous uses of clay make it unique among geological materials and explain the lack of consensus regarding definition (Bergaya & Lagaly, 2006; Gomes & Rautureau, 2021b; Rautureau et al., 2010,

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2017). In general, and from a mineralogical perspective, clay minerals are accepted widely as being fundamental constituents of clay. Every clay needs to have clay minerals in its composition but the minimal quantity is almost impossible to standardize (Gomes, 2021).

The concept of mineral s.s., i.e. natural, inorganic, solid, and crystalline chemical element or compound that participates in the composition of rocks and soils, can be involved in clay–health interactions; this is also true of clay minerals present in both water and air. This should be distinguished from the broader understanding of the term mineral *sensu lato (s.l.)*, which includes: (1) the bio-essential chemical elements of natural and inorganic origin created in soil, and which, in ionic form, are constituents of solid food, of vegetable and animal origin, which are referred to as macronutrients or mineral salts; micronutrients or oligominerals are the main suppliers/carriers of 'minerals' for human nutrition and wellness; (2) the chemical elements, which, in ionic form, are constituents of potable water and referred to as 'minerals,' – mineral water that can also be used in therapies such as crenotherapy, hydrotherapy, and thalassotherapy; and (3) the chemical elements, referred to as 'oligoelements,' which enter the formulations of so-called mineral supplements.

The concept of mineral *s.l.* also includes the derivatives of manipulated and modified clays, such as: (1) delaminated or exfoliated, intercalated, pillared, and acid- or alkaline-activated clay; (2) nanoclays, including some types of clay minerals, e.g. halloysite nanotubes, which have been investigated and are used for the controlled and sustained delivery of drugs; (3) special clays, which are natural associations of minerals dominated by the so-called clay minerals – e.g. hydrous phyllosilicates have been used since Antiquity as cosmetics products and as therapeutic materials for both internal and external applications, as are the geophagy, mud-therapy, and pelotherapy; (4) the hybrid mineral-organic complex, in which the inorganic component is the host, e.g. clay-drug hybrid materials and clay-drug delivery systems, are considered to be very important in the field of applied biomedical research; and (5) synthetic clay minerals which can be used in pharmaceutics and cosmetics (Gomes, 2021).

In health sciences, clays and clay minerals provide essential contributions as active ingredients and excipients in the formulations of both pharmaceuticals and cosmetics, and as constituents, e.g. in polymeric bio-nanocomposites used for biomedical applications such as wound healing, controlled drug delivery, biosensors, medical devices, and tissue regeneration.

The main, traditional areas of clay interest and application, both scientific and technological, are shown in Fig. 1. Specific scientific fields, such as mineralogy, geochemistry, medical geology, medical hydrology, nutrition science, materials science, and nanoscience provide the basic principles and information needed. A large body of literature covers the benefits and risks of clays and clay minerals in terms of human health.

According to Gomes (2018) and Gomes et al. (2021a), the main properties of clays and clay minerals that justify their use in a great variety of therapeutic, cosmetic, biomedical, and medical applications are as follows.

(1) The ubiquity of clay deposits, located at or beneath the Earth's surface, making access and extraction a simple matter.

(2) The extraordinarily small size of clay minerals (usually <2 μm and as small as nanometers) and the anisometric shape of the particles (mostly lamellar, fibrous, tubular, or spherical); both of these characteristics are essential for providing clay with large specific surface areas (commonly between 10 and 300 m^2g^{-1}), a property that is a determining factor when the clay is used in the stomach lining and the small intestine to alleviate heartburn, nausea, bloating indigestion, or for topical coating and adhesion to the skin, or for localized and controlled delivery of drugs. These characteristics may not be beneficial if the clay proves toxic when associated with chronic exposure during inhalation. Clay-mineral surfaces can serve as catalysts for reactions in which, for instance, one organic compound is transformed into another on such surfaces.

(3) Clay minerals have a globally negative electric charge, due mainly to the structural defects (isomorphic atomic substitutions, atomic omissions, and broken/damaged bonds at the edges of the particles). The clay minerals of the kaolin-serpentine group have a small net electrical charge of 0.1–0.2 mV per half unit cell. The clay minerals of the smectite group have an intermediate liquid electrical charge 0.2–0.6 mV per half unit cell, which is responsible for the expansion of the structure (the degree of expansion depends on the nature and hydration capacity of the intercalation cations; these are positioned in the spaces between structural layers and the degree of humidity of the environment in which the minerals occur) and also responsible for the collapse of the structure in a dry environment. The clay minerals of the illite group have a large net electrical charge of 0.6–0.9 mV per half-cell unit which is why they do not expand when hydrated. The overall negative electrical charge of the clay minerals depending on the pH of the environment can be modified (even if compensated and neutralized) by the effect of surface coatings, e.g. of quasi-amorphous or amorphous iron (oxyhydr)oxides of positive electrical charge. Such modifications will have consequences for clay properties, such as ion exchange, plasticity, and rheology.

(4) Poor hardness and abrasiveness are properties that provide a pleasant sensation when a paste of clay comes in contact with the skin and is spread on it.

(5) A high affinity for water makes it easy to form plastic pastes with adequate fluidity, useful for scattering and sticking to the skin and creating a stable dispersion/suspension.

(6) Significant adsorption capacity, a property that allows the adsorption of toxins, bacteria, or viruses and which also allows their elimination from the skin, making an effective remedy for the treatment of skin conditions such as, acne, seborrhea, eczema, psoriasis. Some clay minerals exhibit large adsorption capacities, allowing the incorporation of liquid and solid (inorganic and organic) polar molecules; clay minerals in the smectite group can be

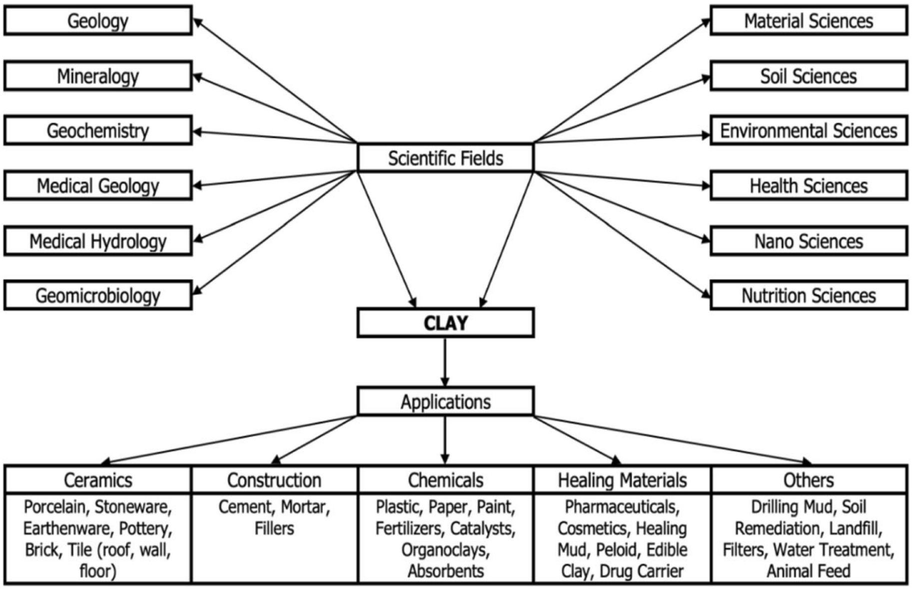

Fig. 1. Scientific fields and traditional areas of application of clays and clay minerals

used as nanocontainers for biologically active species and for the controlled release of drugs at the right target.

(7) The so-called cationic clays, hydrous layered aluminosilicates, are very common in nature and their individual particles or crystals are characterized by negative electrical charge. They can also show a wide range of cation exchange capacity (CEC) from little to significant; the CEC is particularly large in the case of clay minerals with 2:1 structural typology, as is the case for montmorillonite, which can exchange the original interlayer cations for cationic surfactants (quaternary ammonium salts and other organic compounds). These nanostructured hybrids (nanoclays) are gaining increasing interest in the biomedical field.

(8) The so-called anionic clays, also known as hydrotalcites or layered double hydroxides (LDHs), are rare in nature but they can be synthesized easily at low cost. They are characterized by large anion exchange capacity (AEC) values and by other very interesting properties for applications in the field of medicine.

(9) Alkaline-pH clays can neutralize gastrointestinal acidity while acid pH, if close to the pH of the skin, avoids skin irritations.

(10) Clays containing reduced species of exchangeable elements, such as Fe^{2+}, and their oxidative potential are responsible for the bactericidal action of certain clays, e.g. those known as 'French Green Clays,' which become toxic to microorganisms that are pathogenic for humans.

(11) Significant heat-retention capacity and low thermal diffusivity are important characteristics for curative mud/peloid coatings, packs, and poultices that are applied, either hot (up to 45°C) or cold, according to the nature of the disease to treat. The cooling time of the healing mud/peloid (typically 15–20 min from 45 to 37°C) is conditioned by factors such as global composition and clay texture, nature, and quantity of each species of clay mineral, the nature and amount of the associated organic substances, and the nature of the liquid phase (natural mineral water, spring water, sea water, salt lake water...).

(12) Clays are found with a great diversity of natural colors. For white clays, depending on the application, the color can be changed using artificial coloring pigments. White and green clays are preferred for face masks; in pharmaceuticals, e.g. in pills and suspensions, white clay is preferred.

Because of these and other properties, e.g. dispersibility, hygroscopicity, greasiness, plasticity, thixotropy, biocompatibility, and quasi-innocuousness (in a few cases clay and clay minerals could be hazardous), clays and clay minerals are used widely in the pharmaceutical industry as active substances. In particular, they are used as excipients acting as lubricants, desiccants, disjoiners, diluters, stabilizers, binders, opacifiers, pigments, emulsifiers, and thickeners, as isotonic and anticaking agents, and they can also be used as a flavoring agent and active drug carrier (Awad et al., 2017; Carretero 2002; Carretero & Pozo 2009, 2010; Carretero et al., 2013).

POSITIVE AND NEGATIVE INTERACTIONS BETWEEN CLAYS AND CLAY MINERALS AND HUMAN HEALTH

Clays and the clay minerals are used widely in both the pharmaceutical and cosmetics industries, particularly because of properties such as electrical charge, large specific surface area, large adsorption capacity, ion exchange capacity, and little or no toxicity. Among the various species of clay minerals, kaolinite, halloysite, talc, and smectites (montmorillonite, sepiolite, saponite, and hectorite), sepiolite and palygorskite are the most used in pharmaceutical applications as active ingredients and particularly as excipients acting as diluents, lubricants, binders, disintegrants, flavor correctors, and as thickening, anticaking, and emulsifier agents (Carretero, 2002; Carretero & Pozo, 2009, 2010; Carretero et al., 2013; Gomes et al., 2021b; Lopez-Galindo & Viseras, 2004; Lopez-Galindo et al., 2007, 2011; Viseras & López-Galindo, 1999, 2000; Viseras et al., 2001).

Among other natural materials used for human health care, clays and clay minerals have the ability to penetrate the various natural barriers of the body through the following pathways: ingestion, inhalation, and skin absorption.

Recent research has reinforced the potential applications of clays and clay minerals in the pharmaceutical, biomedical, and cosmetics fields. Among all clay-mineral species, those used most for pharmacological applications are kaolinite, halloysite, montmorillonite, talc, palygorskite, and sepiolite. Some can be used in formulations to be appl.ied as antacids to reduce gastric acidity, as gastrointestinal protectors, and as antidiarrheals. Others are used extensively as excipients in some formulations, acting as diluents, binders, emulsifiers, and carriers of biologically active molecules for improving drug availability (Kim et al., 2016; Massaro et al., 2018; Gomes et al., 2021b).

The present paper shows some cases of both positive and negative interaction between clays/clay minerals and human health.

Geophagy

Geophagy, the old tradition of eating clay and clayey soil, is still practicsed in many countries, particularly in Africa, Asia, and South America. In Europe there are a few written references indicating that, between the 16th and the 18th centuries, so-called pucarophagy (Portugal) and bucarophagy (Spain), i.e. the eating of pieces of broken red clay from pottery containers used for drinking water, was practiced by people belonging largely to the wealthy classes.

Geophagy was used to compensate for nutritional deficiency. The available literature on geophagy includes: Abrahams (2002, 2005, 2012, 2013), Arhin and Zango (2017), Bonglaisin et al. (2017), Diko and Diko (2014), Gomes (2018), Gomes et al. (2021a), Huebl et al. (2016), Kikouama and Baldé (2010), Kmiec et al. (2017), Kutalek et al. (2010), Miller et al. (2018), Seim et al. (2013), Solaini et al. (2012), Wilson (2003), and Young and Miller (2019).

Definition, Geographies, Benefits, and Risks

Definition and Geographies. Geophagy was first reported by Aristotle (384–322 BC) and further described by Dioscorides and Avicenna in 40 BC and 1000 AD, respectively. One of the first reports on geophagy was from Von Humbolt, who wrote in his travel reports from South America between 1799 and 1804 that clay was eaten to some extent at all times by the Otomac tribe along the Orinocco River, and in Peru he saw mothers give their children lumps of clay "to keep them quiet" (Halsted, 1968). Geophagy is practiced by humans and other animal species of all geographies, and is documented widely. The causes and consequences of geophagy, particularly for children and pregnant women, remain poorly understood, however.

Based on the available information, geophagy provides health benefits and risks through four mechanisms of action: protective, buffer and antacid, chemical-element release, and restoration (Rautureau et al., 2017; Gomes 2018, Gomes & Rautureau 2021a). The authors referred to here have summarized the benefits and risks as follows:

Benefits. Gastroenterological diseases (diarrhea, colitis, nausea, colonopathy, and ulcers); and sources of mineral nutrients (dietary supplementation, e.g. in the case of Fe, Zn, and Mg deficiencies).

Risks. Microbiological contamination (pathogenic microorganisms, present in natural geomaterial and/or acquired during its manipulation, baking not being sufficient to remove their threat); contamination by toxic trace elements (Pb, Cd, Hg, Al, As, etc.) through enteric incorporation; and constipation and reduction of the gastrointestinal absorption capacity of drugs taken simultaneously with the edible clay).

The name edible clay is applied to clay that is chewed deliberately and ingested by humans as cookies and small lumps, or ingested as clay/potable water dispersions/suspensions. Lumps of clay can be bought in open markets and in some convenience shops. The clay can act as a source of mineral micronutrients and as protective material against pathogens and toxins (detoxification of noxious or unpalatable compounds present in the diet); the clay can also act as an antacid for gastric acidity (Rautureau et al., 2017). Experience shows that the mineralogical and chemical compositions of 'edible clays' are the conditioning factors of adsorbent and absorbent power and also the alkalinity of these clays, which justify the health benefits of their users.

Pica is defined as the purposive consumption of substances that are not generally identified as food. For Danford (1982), pica encompasses geophagy (earth eating), amylophagy (consumption of raw starches), and pagophagy (consumption of ice). Several aetiologies of pica have been proposed, including hunger, micronutrient deficiencies, gastrointestinal distress, and increased exposure or susceptibility to pathogens (Young et al., 2008; Young, 2010).

Bucarophagy and Pucarophagy

As noted above, bucarophagy (Spain) or pucarophagy (Portugal) was practiced by wealthier people who consumed, not only soil, but also clayey soil and clay. Clay-based materials that had undergone low-temperature firing modification, e.g. in the case of red-ware ceramics of pottery typology, i.e. terracotta, were also consumed in the Iberian countries, from the Middle Ages to the Early Modern Age. The terms bucarophagy and pucarophagy are attributed to small ceramic pottery of generally <1 L capacity and which were used for cooling and scenting drinking water. Bucarophagy and pucarophagy date back to the 9th century; in fact, possibly following Arabic conquest; the Arabs probably acquired the custom from Persia.

The custom of eating *púcaros* and *bucaros* was maintained up to the 19th century. Bucarophagy and pucarophagy were

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popular in the Iberian Peninsula, and beginning with the 17th century, similar ceramic containers or vases produced in various Spanish American colonies of the so-called East Indies had been exported to southern European countries, especially Spain and Italy (Domenici, 2019; Garcia-Rodriguez & Álvarez-Garcia, 2019; Rovira & Gaitán, 2010; Seseña, 2009; Vasconcellos, 1905). The health benefit of eating *púcaros* and *bucaros* would have been for anemia problems that could be compensated by the ingestion of the Fe-rich ceramic raw materials. Examples of these Fe-rich raw materials, in the case of Portugal, are terra-rossa soil, the result of marble weathering in the regions of Estremoz, Borba, and Vila-Viçosa in Alentejo, Portugal (Alves, 2015; Alves et al., 2016; Cunha, 2010); and red clayey soils from limestone and basalt weathering in the region of Lisbon, Portugal. It is assumed that these were used in small, local pottery units for the manufacture of *púcaros*. The Portuguese *púcaros* could have preceded the Spanish *bucaros* and, as a rule, they display a poorly burnished red surface, with or without decoration, a common characteristic of all these small ceramic containers which actually can be found in some museums. A *bucaro* as represented by the artist Diego Velázquez in his well-known painting 'Las Meninas', is currently being exhibited in the Museo del Prado in Madrid, Spain.

Animal Feed

Interest is growing in mineral additives to animal feed. Commercial-grade clays such as bentonite, kaolin, and sepiolite, which are characterized by large adsorption capacity and non-toxicity, are used as feed additives for all animal species (beef and dairy cattle, poultry, pigs, etc.). The main function of these feed additives is to bind toxic metabolites and mycotoxins. Contamination of food and feedstuff by mycotoxins is a worldwide problem for corn, wheat, barley, oats, and other crops. Animal feeds containing mycotoxins cause significant losses in livestock production and pose risks to human health, because aflatoxins are poisonous chemicals produced by molds. The toxicity of molds can be reduced by using clay additives which have potential additional benefits for animal health as well for the safety of human food (Coffey & Dawson, 2015; European Food Safety Authority, 2017; Jaynes & Zartman, 2011; Maki & Haney, 2017; Nadziakiewicza et al., 2019; Slamova et al., 2011).

Regarding aflatoxins, dozens of publications have been produced over decades of study at the Texas A&M University. A distinguished member at that Institution, Phillips (1999) discovered early that clays can be added to a diet without harmful effects, to prevent the human digestive system from adsorbing the aflatoxin. It is estimated that up to 10% of the world's animal feedstuff now contain a clay-based sorbent. Work continues on the selection and modification of smectite clay minerals in order to improve the binding efficiency of aflatoxin (Gan et al., 2018).

Bentonite and the clay minerals of the smectite group, especially montmorillonite, because of their ability to form thixotropic gels with water, can adsorb large quantities of gas and interlayer, bioactive, cationic agents which offer antibacterial activity that could be used in the design of biomaterials and for therapeutic purposes. On the other hand, the toxicology of clay minerals and their derived nanocomposites have also been evaluated (Mainsanaba et al., 2015).

Pharmaceuticals and Cosmetics

Many publications exist about the important roles of specific clays and clay minerals in pharmaceuticals and cosmetics (Gomes et al., 2021b). Clays and clay minerals have the ability to penetrate the various natural barriers of the human body via ingestion, inhalation, and skin absorption.

Pharmaceuticals. Clay minerals have been used as active ingredients in pharmaceutical products, both for the administration (orally and/or topically) and for therapeutic activity. The authors emphasize the role of some clay minerals in the following functions: gastrointestinal protectors (kaolinite, montmorillonite, saponite, hectorite, sepiolite), antidiarrheics (kaolinite, montmorillonite, palygorskite, sepiolite), and hemostatic agents (kaolinite is a component of common, commercial wound-dressing products) (Carretero et al., 2013; Chang et al., 2007; Li et al., 2012; Williams et al., 2008). Kaolinite could intervene favorably in the coagulation mechanism, creating a physical mesh that facilitates platelet aggregation and coagulation (Glick et al., 2013; Smith et al., 2013). Combat Gauze ™, a non-woven gauze impregnated with kaolin, has replaced other clay-based hemostatic dressing products, and is the only product of its kind endorsed for use in the first-line treatment of life-threatening injuries.

Clay-mineral surface properties are also of prime importance in medical applications. In the last few decades some clay minerals, especially halloysite, montmorillonite, sepiolite, and palygorskite, based on fundamental and clinical research, have been considered effective carriers of active drug molecules providing useful applications in the pharmaceutical industry (Carretero & Pozo, 2009, 2010; Lvov & Price, 2008; Lvov et al., 2008, 2016; Massaro et al., 2018; Viseras et al., 2019). Clay minerals also play an important role in drug encapsulation (Delcea et al., 2011; Yapar et al., 2017), in drug-delivery systems (Kinninmonth et al., 2014); in the formation of antimicrobial surfaces (Babu et al., 2018; Nigmatullin et al., 2009) in the release of active substances (Favero et al., 2016); and in drug efficiency (Ambrogi et al., 2014). Some clay minerals, such as montmorillonite, are efficient sorbents of various types of drugs, such as antibiotics, photosensitizers (Donauerová et al., 2015), or disinfectants (Calabrese et al., 2016, 2017).

Organoclays are clays or clay minerals modified by exchanging the original interlayer cations in the 2:1 clay mineral structure, particularly in montmorillonite, for organic cations, typically quaternary alkylammonium ions, through treatment with quaternary ammonium salts generating organophilic surfaces (De Paiva et al., 2008; Guégan, 2019; He et al., 2014; Yariv & Cross, 2002). Organoclays have been tested as antimicrobial and disinfection agents (Hong & Rhim, 2008; Bragg et al., 2014; Yuen et al., 2015). Organoclays are also used to produce polymer-clay nanocomposites enabling the adsorption of organic contaminants in pesticides and herbicides, and in cosmetics and pharmaceutics, which are found increasingly in water resources in spite of wastewater treatments. Organoclays are used in medicine (Ambre et al., 2010; Suresh et al., 2010; Sandri et al., 2020), in cosmetics, and in pharmaceuticals (Patel et al., 2006). Organoclays, either individually or in composites with polymers, have been used in the formulation of biomedical applications (Ghadiri et al., 2015).

Montmorillonite nanoparticles have been involved in studies such as: drug-carriage and release; antimicrobial activity; antacid activity; and wound healing (He et al., 2014, 2015; Hosseini et al., 2018; Krishnan & Mahalingam, 2017; Merino et al., 2018; Verma & Riaz, 2018). Clay-drug hybrid materials have important biomedical applications as drug-delivery systems. Montmorillonite in the form of nanocomposite hydrogels as in the case of gelatin-metacrylol(GelMa) hydrogels, is being applied in tissue engineering and regenerative medicine (Mousa et al., 2018; Nones et al., 2015; Shin et al., 2013; Xavier et al., 2015).

Synthetic analogues of clay minerals of simple composition have been and are being produced in laboratories, along with the so-called modified and clay-based composites: organoclays, clay-polymer hybrids, clay-drug hybrids, and hydrogels, so that they can better fulfil particular biomedical applications in wound healing, drug delivery, hard- and soft-tissue regeneration, biosensing, and bioassays (Ghadiri et al., 2015; Oliveira et al., 2018; Ruiz-Hitzky et al., 2010, 2015, 2017; Sandri 2020; Wu et al., 2010).

For synthetic clay minerals, the potential of Laponite® as a nanomaterial in the fields of drug delivery, bio-imaging, tissue engineering, and regenerative medicine was highlighted by Tomás et al. (2018).

Because of the physical and physicochemical properties of kaolinite, smectites, talc, palygorskite, and sepiolite, and because of their biocompatibility, they are used worldwide as inactive components in non-parenteral (oral and topical) administration, i.e. as excipients in pharmaceutical formulations having the following aims: (1) to improve the organoleptic characteristics of the formulation, such as taste and color, through the incorporation of flavor-correcting minerals and chromatic pigments; (2) to improve the physicochemical characteristics of the formulation, such as viscosity and suspensibility of the active substance, through the incorporation of minerals with thickening and emulsifying action; (3) to facilitate preparation of the formulation through the incorporation of minerals with lubricating action and diluent; (4) to facilitate preparation of the formulation through the incorporation of minerals with desiccant action; and (5) to facilitate the release of active substances into the body through release by the minerals carrying that substance.

Specific clay minerals serving as excipients can act as lubricants (talc), taste correctors (smectite, palygorskite, and sepiolite), disintegrants (smectite, palygorskite, sepiolite), diluents (talc, kaolinite, smectite, palygorskite, and sepiolite), binders or agglomerants (kaolinite and montmorillonite), emulsifiers and thickeners (smectites, palygorskite, sepiolite, and kaolinite), and as flavor correctors (smectites, palygorskite, and sepiolite).

In the past 10–12 years, clay mineral-based systems have been developed as carriers for controlled release of drugs (antibiotics, anticancer, antibacterial, antimycotic, anti-inflammatory, antioxidant, etc.). Specific clay minerals, such as halloysite, montmorillonite, sepiolite, and synthetic clay-like minerals (e.g. layered double hydroxides) are used in the clay-drug hybridization process by solution or melting intercalation (Ghadiri et al., 2015).

Cosmetics. Clays and clay minerals are used extensively in cosmetics, for skin-care and for beauty purposes. Clays and clay minerals are used in cosmetics because they are natural, and, if used in appropriate amounts, are harmless (Carretero, 2002; Carretero et al., 2006, 2013; López-Galindo & Viseras, 2004; López-Galindo et al., 2011). A typical cosmetics product contains many ingredients, and most cosmetics contain a combination of at least the following ingredients: water (distilled or sterilized), emulsifier, thickener, emollient, color pigment, fragrance, preservative, and pH stabilizer. As excipients in cosmetics, clays and clay minerals are used widely to stabilize emulsions and suspensions, and to modify the rheological behavior of these systems; they also play important roles as adsorbents and absorbents (Moraes et al., 2017). Clays and clay minerals, when used in cosmetics formulations (e.g. in facial masks) provide the following properties: (1) softness and small particle size, as the application of the clay-paste, especially in the form of a face mask, can otherwise be unpleasant; (2) appropriate rheological properties for the formation of a viscous and consistent paste; good plastic properties for easy application, and adherence to the skin during treatment; (3) similar pH to the skin to avoid irritation or other dermatological problems; (4) significant adsorption capacity; clays can eliminate excess grease and toxins from the skin, and hence are very effective against dermatological diseases such as boils, acne, ulcers, abscess, and seborrhea; an active organic principle can also be incorporated into the clay mineral before its application to the patient's skin for therapeutic and cosmetics purposes; (5) large cation exchange capacity (CEC), enabling an exchange of nutrients (K^+, Na^+, Ca^{2+}, Mg^{2+}, or others) to take place while the clay mineral is in contact with the skin; and (6) high heat-retention capacity (retentiveness); because heat is a therapeutic agent, clay-paste is applied while warm to treat chronic rheumatic inflammations, sports traumatisms, and dermatological problems.

Chemical and Microbiological Safety of Clay-Based Pharmaceuticals and Cosmetics

Clays are natural chemical systems of greater or lesser chemical complexity, which are formed at or near the Earth's surface in environments sometimes modified and polluted anthropogenetically. In general, metals are constituents of clays and of their associated natural compounds, both inorganic and organic, and the so-called heavy metals, in particular, are recognized for their toxicity, even in trace concentrations. Such metals are either constituents of non-clay minerals and clay-mineral structures, or are adsorbed in a reversible way at electrically charged, external, clay-mineral surfaces. Organic

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matter and the commonly associated pathogenic microorganisms are also associated with clays. As a rule, before the formulation of clay-based healthcare products, clay undergoes fine processing (refining, beneficiation, and sterilization), which can reduce the amount of potentially toxic chemical elements and pathogenic microorganisms.

Only in recent decades has it been recognized scientifically that some topically applied substances may penetrate human skin, and systemic exposure may cause toxicity (Loretz et al., 2006; Nohynek et al., 2010). Clays and clay minerals participate in the formulations of many cosmetics which are mainly applied topically. Ingestion and skin absorption are known as the main pathways for the incorporation of toxic elements and compounds, and is the reason why the sanitary safety of clay-based products for therapeutic and cosmetic applications is essential. On one hand, when clay is ingested, the potentially toxic elements (e.g. heavy metals and their compounds) within the clay structure could become bioavailable if the clays undergo total or partial acid-dissolution inside the stomach; on the other hand, those metals adsorbed at the clay-mineral surfaces are easily bioavailable and incorporated, but their concentrations could be reduced or even eliminated if the clay had been submitted to appropriate acid chemical leaching and cation-exchange processing.

The use of clay minerals in health-care products, drugs, and cosmetics is based on ancestral knowledge but nowadays the manufacture of drugs and cosmetics faces modern scientific demands and sanitary requirements, which sometimes impose the rejection of some products in circumstances that could look like a kind of 'chemophobia'. The accomplishment of increasingly drastic standards justifies the modern preference for synthetic compounds over natural ones. The solution consists of looking for either other sources of purer materials (which is not always possible) or for limits to their use imposed by regulations. This, effectively, is the medically difficult concept of benefit and risk. Significant progress is being made due to the work of physicists and physical chemists, particularly in the field of nanomaterials.

To be suitable for pharmaceutical or cosmetic applications, clays must comply with a number of chemical (stability, purity, chemical inertness), physical (texture, particle size, water content), and toxicological (toxicity, safety, and microbiological purity) requirements (Cerezo et al., 2006; Delgado et al., 2020; López-Galindo & Viseras, 2004; López-Galindo et al., 2007, 2011; Tateo & Summa, 2007; Viseras et al., 2007). Specifically, clays must have little or no toxicity. According to Delgado et al. (2020), carcinogenic fibrous minerals (asbestos) could be associated with talc due to the natural origin of this hydrous Mg-based phyllosilicate used as protective, lubricating, and refreshing material; asbestos is banned from pharmaceutical and cosmetics grades of talc powder employed in cutaneous applications, and talc purity of at least 90% is required. According to Roselli et al. (2015), the fundamental property that needs to be considered and maintained in any material used for pharmaceutical and cosmetics purposes is that it should have little or zero toxicity.

Concerning pharmaceutical products, the ICH guideline Q3D on Elemental Impurities (EMA/CHMP/ICH 353369/2013) indicates the maximum PDE (Permitted Daily Exposure) acceptable for the daily intake of elemental chemical impurities existing in pharmaceuticals, drug products, and active ingredients and excipients for oral, parenteral, and inhalation exposures.

A review of the various Pharmacopoeias, rules, and regulations affecting the use of natural clays was written by López-Galindo et al. (2007). For microbiological safety, which depends on eventual contamination of microorganisms during processing, manufacture, and storage, EU and US Pharmacopoeias established microbial limits, expressed in CFU/g of aerobic bacteria and fungi.

Given that clays and clay minerals are used extensively in cosmetics, the definition of cosmetics product was established in Europe by the Council Directive 76/768/EEC, and in the USA by the Food and Drug Administration (FDA). The European Community Directive 2001/83/EC defines medicinal products for human use. EC Regulation 1223/2009 which came into law on 11 July 2013 establishes the sanitary safety of cosmetics in terms of the quality and quantity of heavy metals. The SCCS (Scientific Committee on Consumer Safety) has proposed revisions to Regulation 1223/2009, the so-called 'SCCS Notes of Guidance for the Testing of Cosmetics and their Safety Evaluation,' the 9th revision of SCCS/1564/15 being issued on 29 September 2015. Cosmetics products must not contain heavy metals such as Pb, Cd, As, Sb, Hg, and their compounds. Article 17 of the Regulation states that the unintended presence of heavy metals in cosmetics is allowed only if it is technically unavoidable under good manufacture practices, and if the products are still safe for human health.

Regarding toxic metals and their compounds present in cosmetics, Bocca and Pinto (2014) published an interesting review about the limitations which are imposed at present in the USA, Canada, and Europe; those authors concluded that further research on cosmetics safety is mandatory. For drug and cosmetic products, the EMA (European Medicines Agency, 2008) and Health Canada (HC-SC 2011, 2012) imposed strict chemical limitations. Also, European Pharmacopeia (2011) and US Pharmacopeia (USP 32-NF27, 2009) imposed chemical limitations for heavy metals (total content) and for As and Pb concentrations. According to the European Norm 1223/2009, the European Commission [EC] (2009) states that As, Se, Cd, Hg, Pb, Sb, Tl, and its compounds are not permitted in cosmetics products. Guidance on the safety assessment of the ingredients of cosmetics has been published by the EU Scientific Committee on Consumer Products (Scientific Committee on Consumers Products, 2012); its Annex II contains a list of substances that should not be present in the compositions of cosmetics products. The German Monitoring Scheme data basis established the technically avoidable heavy metal limits in cosmetics products, expressed here in mg/kg: Pb – 2.0, Cd – 0.1, Hg – 0.1, As – 0.5, Sb – 0.5 for products such as make-up powder, rouge, eye shadow, eye-liner; and Pb – 0.5, Cd – 0.1, Hg – 0.1, As – 0.5, Sb – 0.5 for toothpaste (BVL, 2017).

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Clays are usually sterilized by heating at >160°C for not less than 1 h or by exposure to gamma radiation (Bubik, 1992). For clay used in cosmetics formulations proposed for sterilization, the following method was proposed by Favero et al. (2016): (1) immersion in ethanol 70% (m/m) (58.61g ethanol 96% +27.08g distilled water) at 1:10 (m/m) clay/solvent ratio, for 10 min under manual stirring; (2) filtration under reduced pressure; and (3)oven-drying at 120°C, for 24 h. The efficacy of the method employed was checked with the following pathogenic bacteria: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and with molds and yeasts. Kaolin, for example, could be sterilized by heating at 200°C for 1 h without any change of its fundamental properties (Gomes et al., 2020).

Peloids and Pelotherapy

As a basic component of the so-called healing muds and peloids, clay plays an important role in the external or topical applications known as 'mud therapy' and 'pelotherapy'. Healing muds and peloids are two-phase systems consisting of a solid phase (clay-based, as a rule) and a liquid phase (natural mineral water-based, as a rule). Healing mud or natural peloid, and peloid or peloid *s.s.* or peloid itself are firstly characterized, differentiated, and classified on the basis of their natural origin, chemistry (inorganic and organic components), mineralogy, texture (grain-size distribution), as well as physical (spreadness, adhesiveness, hardness), rheological (apparent viscosity and thixotropy), and thermal properties (heat capacity, specific heat, and cooling rate). Healing muds or peloids are applied either at the natural occurrence site in the case of healing mud, or inside the spa facilities in the case of peloid which corresponds to a healing mud that undergoes manipulation and modification particularly by maturation in artificial conditions. The healthcare assets of healing muds and peloids depend mainly on the nature and quantity of the liquid phase. A large number of publications dealing with the aforementioned properties is available (Armijo, 1991; Armijo et al., 2016; Carretero, 2020a, 2020b; Carretero et al., 2006, 2013; Cerezo et al., 2006; Fernández-Gonzalez et al., 2013, 2017; Ferrand & Yvon, 2000; Gamiz et al., 2009; Gomes, 2013, 2015, 2018; Gomes et al., 2013, 2021b; Khiari et al., 2014; Legido et al., 2007; Legido & Mourelle, 2008; Maraver et al., 2021; Rebelo et al., 2011; Tateo et al., 2010; Veniale et al., 2004; Viseras et al., 2006). In particular, the publications by Carretero (2020a, 2020b) are very extensive reviews which show and discuss the outcome of hundreds of studies and publications involving researchers specialized in relevant disciplines, such as geology, mineralogy, chemistry (inorganic and organic), physics, physics-chemistry, microbiology, and medicine (medical hydrology and toxicology). Of those publications considered here, most (hundreds) have dealt with the properties of both the peloid solid phase (clay in the majority of cases) and the peloid liquid phase (mineral medicinal water from thermal resort spas), and very few (tens) have dealt with peloid-application benefits (temporary anti-inflammatory effects) on people suffering from musculoskeletal diseases (osteoarthritis, rheumatoid arthritis, and psoriatic arthritis, and lower back-pain). The therapeutic efficacy was not demonstrated fully, nor were the mechanisms of therapeutic action fully identified.

The name peloid is derived from the Greek word πξλος spelled pelòs, meaning mud, and from the name peloid, the terms peloid therapy and pelotherapy were derived. The designation 'peloid' was adopted definitively at the Conference of the ISMH (International Society of Medical Hydrology) held in Wiesbaden, Germany, in 1938. Peloid was then defined as: 'Natural product (natural sediment) composed of a mixture of mineral water (sea water and lake water included) with organic or inorganic matter which results from either geologic or biologic processes or both, and is utilized for therapeutic purposes in the form of packs, compresses, or baths.' This is the official international definition of peloid that was approved in the IV^{ème} ISMH Conference held in 1949, in Dax, France. Dax was the first and still is the main principal thermal resort town in France and is frequented by ~55,000 patients/year.

Recognizing that manipulation, modification, and maturation are essential in developing the healing and/or cosmetics properties of a peloid, a new definition of peloid was proposed by Gomes et al. (2013): "Peloid is a maturated mud or muddy dispersion with healing and/or cosmetic properties, composed of a complex mixture of fine-grained natural materials of geologic and/or biologic origins, mineral water or sea water, and commonly organic compounds from biological metabolic activity."

Peloid healing properties are currently recognized by Medical Hydrology professionals who prescribe and supervise peloid application.

The IV^{ème} ISMH Conference also approved the official International Classification of Peloids which is based on: (1) the origin of the solid component; (2) the chemical nature and temperature of mineral water; and (3) the maturation conditions.

The original classification of peloids, in French, contains the following typologies: boue (mud, fanghi, schlam, barro, argila); limon (loam, slime, ooze, limo); tourbe (peat, moor, torbe, turfa); muffe (mousse, barégine); bioglée (bioglea, biofilm); sapropeli (sapropel); and gyttia (nekron mud).

For their general composition, peloids can be classified as follows: (1) essentially inorganic; (2) essentially organic; (3) mixed inorganic-organic (Gomes et al., 2013).

Clay participates in all three typologies and is the major component of the inorganic matter. Peloids are divided into two classes: (1) primary peloids or virgin peloids are healing muds in which the solid component has been transported mechanically as dispersed particulate matter in spring mineral water and deposited thereafter; (2) secondary peloids are healing muds where the solid component and the mineral water come from different sources (Veniale, 1996, 1998, Veniale et al., 2007).

For application purposes, peloids are divided into two categories: (1) medical or therapeutic peloids; and (2) cosmetic peloids (Carretero, 2002; Gomes et al., 2013, 2021b; Gomes, 2018).

Peloids are either natural clay-water mixtures which have undergone a maturation process at a Health spa, or are natural

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clay-water mixtures in which the natural liquid phase has been replaced by natural mineral water used in a Health spa (thus becoming specific to that spa). Peloids may also be controlled triple-mixtures of specific clay-specific mineral water-specific natural-synthetic functional additives. These are referred to as "tailored or designed and engineered peloids", as they are designed, manipulated, and modified to fulfil certain medical functions (musculoskeletal and dermatological) or cosmetics functions, and could be prepared at spa facilities or in a related manufacturing unit (Gomes, 2015, 2018; Gomes et al., 2021a).

The healing mechanisms of peloids are currently defined as thermotherapeutic, chemotherapeutic, and biological and biochemical (Gomes, 2015; Gomes et al., 2013, 2021a; Maraver, 2006, 2017; Maraver et al., 2015; Matas et al., 2014; Meijide et al., 2014, 2015; Rautureau et al., 2017; Roques, 2015). Some authors enhance the action of the peloid liquid phase (in particular, the so-called interstitial water that corresponds to the equilibrium product from the interaction between natural mineral water with the solid phase, especially with its clay component and cationic exchange) relative to the peloid solid phase (Carbajo & Maraver 2015, 2016, 2018; Fernández-González et al., 2013, 2021; Gomes, 2015).

Sea-saline mud and salt-pan mud as sea-derivative products have been and still are used in Thalasso Centers to treat various health disorders. The Dead Sea is a model natural Thalassotherapy and Climatotherapy Center, because its saline mud is used, either in the natural state, or after manipulation as an ingredient into formulations for the treatment of dermal (psoriasis) and other aesthetic considerations (Abu-Shakra et al., 2014; Coddish et al., 2005; Gomes et al., 2019a; Portugal-Cohen et al., 2009).

'Designed and Engineered' Peloid: Preparation Method and New Developments

Peloid therapy or pelotherapy is based on natural peloid or healing mud matured at the site of occurrence, or, for peloid *s.s.* or manipulated and modified peloid matured at spa facilities, located near the natural occurrences.

Interest in natural peloids is waning in favor of therapy based on secondary peloids which have undergone manipulation and modification (refinement, beneficiation, and maturation) before use in spas, for the following reasons. (1) Access to natural peloids has become increasingly difficult due to environmental restrictions; natural peloid deposits are, as a rule, located in 'protected' areas. (2) The geologic sites where natural peloids occur are open systems highly vulnerable to anthropogenic contamination, particularly due to pathogenic microorganisms; the vulnerability could also be due to potential toxic inorganic and organic compounds resulting from nearby urban, agricultural, and industrial activities. The situations referred to here would make the sanitary control and safety of natural peloids very difficult or impossible. (3) The use of natural peloids could be hazardous, e.g. mud deposited by acidic volcanic waters which have low pH (2–3), and are naturally aggressive to human skin. They usually contain relatively large amounts of heavy metals. (4) The complexity of the composition and characteristics of natural peloids makes it difficult to identify the active healing components, and also to understand the mechanism of healing. Control of both composition and sanitary state is also difficult. These reasons mean that there is justified interest in peloid therapy based on manipulated and modified peloids, particularly for those referred to as 'designed and engineered,' the formulations of which could be based on a chemically and microbiologically controlled mixture of a particular clay with a particular natural mineral water mixture to which functional additives (natural or synthetic) can be added.

A 'designed and engineered' peloid is a modified peloid produced at specialized manufacturing units for use at health spas, or produced on-site at the spa itself. In both cases, the products could be designed and manipulated to comply with both the therapeutic and cosmetics goals and functions anticipated. 'Designed and engineered' peloids are a variant of the so-called extemporaneous peloid which, by definition, is prepared at the location and time of use, blending special clays such as kaolin or bentonite with natural mineral water, spring water, or seawater, and involving either a very short-term maturation or no maturation at all. This would not be considered a real peloid *s.s.*

The effects on mechanical and functional characteristics of skin caused by the application of extemporaneous peloids (based on bentonite mixed with both sulfurous thermal water and seawater), as well as the clinical effects, expressed as skin exfoliation, were studied and assessed by Meijide et al. (2010) and Arribas et al. (2010). 'Designed and engineered' peloids are distinguished from extemporaneous peloids as they require short-term maturation of no more than 1–2 weeks, the time required to obtain sufficient physical, chemical, and eventually biochemical equilibrium among all the peloid constituents. Maturation is considered to have been accomplished as soon as the peloid interstitial liquid phase has become chemically stable following the modification of the chemical signature of the natural mineral water being used, the clay having contributed to that stability through its specific cation and anion exchange properties.

'Designed and engineered' peloids can be manufactured easily, using, for example, specific mixtures of an almost monomineralic commercial clay, e.g. kaolin or bentonite, preferably of pharmaceutical grade, with a specific mineral water, e.g. seawater and salt-lake water, or natural mineral water, e.g. spring thermal water. These mixtures, having undergone manipulation and maturation, could be beneficiated, such as through the incorporation of functionally active healing additives, either natural (e.g. the natural polymers chitin, chitosan, starch, gellan gum, and aloe vera) or synthetic, both characterized by analgesic, anti-inflammatory, anti-bacterial, anti-oxidation, anti-cellulite, anti-psoriasis, and anti-acne properties. Chitosan, in particular, is the second most abundant biopolymer on Earth after cellulose, and is distributed widely in crustaceans and insects, being extracted either from crab and shrimp shells or from vegetables. It is a natural, cationic polymer, which is non-toxic, biocompatible, and biodegradable, and which has been the subject of much investigation. Chitosan has been used as a topical dressing for wounds and

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burns due to its hemostatic and other properties, and was previously referred to as chitosan-based nanohybrid membranes or chitosan/montmorillonite biocomposites (Dai et al., 2011; Moghadas et al., 2016; Onnainty et al., 2016; Rabea et al., 2003). As a rule, the natural mineral waters used in the preparation of 'designed and engineered' peloid formulations emerge as natural thermal springs at the territories of thermal spa resorts, where health-resort medicine is practiced.

Chemical and Microbiological Safety of Peloids

No official guidelines exist with respect to the chemical safety of medical peloids. The academic community used to follow the standards specified by the US Pharmacopoeias, considering that peloids have similarities to pharmaceuticals. In the European Union, no unilateral agreement exists for the microbiological identification of healing mud and peloid, in spite of the concern shown by the European Spas Association (ESA), which has considered establishing quality criteria for spring medicinal waters and for thermal peloids (during the ESA General Assembly, 2006, held at the Thermal Resort of São Pedro do Sul, Portugal). The ESA did not define quantitatively standards or guidelines for either chemical or microbiological contaminants in natural mineral water, spring water, or peloids used in balneology – the study and therapeutic use of mineral medicinal waters and of healing muds and peloids. The European Regulation, EC n° 1223/2009, recommends particular attent to the microbial purity of topical products (cosmetics) being used on mucous membranes in general, and on damaged skin in particular.

Microbiological safety is as important as chemical safety. Amongst European countries, with the exception of certain regions of Germany and France, no quality standards or guidelines for muds or for peloids utilized for therapeutic purposes exist. As far as microbiological risks are concerned, besides their autochthonous or natural microflora, natural peloids and peloids *s.s.* could have an allochthonous microflora of medicinal importance (e.g. thermophilic microorganisms such as diatoms and cyanobacteria) involved in the maturation process, providing the release of therapeutically active biogenic compounds with anti-inflammatory and antioxidant properties (Galzigna et al., 1996; Gris et al., 2017; Marcolongo et al., 2006; Tolomio et al., 2004). These may pose risk because they may include undesirable pathogenic microorganisms, mostly of anthropogenic origin. The microbiota community of ~50 matured muds from 29 thermal spas (from a total of ~100 such spas) used for therapeutic purposes in the Euganean Thermal District (NE Italy) were studied by Gris et al. (2020). These spas are internationally renowned since ancient times for the beneficial effects of both the thermal waters and muds on human health. The Euganean Thermal District where famous thermal spas, such as Abano Terme, Montegrotto Terme, and Battaglia Terme are located, is one of the most important thermal territories in the world for thermal water baths and mud treatments used to treat rheumatic diseases such as arthritis and osteoarthritis. Of volcanic origin, the Euganean Thermal District is characterized by a hydrothermal basin rich in hypersaline (high values of TDS, from 2.3 to 6 g/L) and hyperthermal (~75°C) waters flowing to the surface through natural springs and artificial boreholes, and bearing in solution Cl, Na, K, Mg, S, Br, and I as the principal elements. As a rule, peloids are obtained from natural muds extracted from the bottom clayey sediment ('virgin clay') of local lakes (Lispida and Arquà lakes), and afterwards matured for periods up to years in special and artificial maturation ponds or tanks. The thermal mud treatment consists of the application of warm muds directly on patient skin for healing rheumatic diseases. Each spa uses the thermal water from its own thermal well or borehole, and thus produces an exclusive peloid. Peloid preparation follows the regional regulation (BUR 2015); the 'virgin mud' used in pelotherapy must be matured independently by each individual spa. Thermal muds gain their therapeutic properties during the maturation process in which mud is blended with thermal water under specific conditions providing a characteristic microbial and cyanobacterial population composition. A mud's Chlorophyll α (Chl α) content is utilized conventionally as a practical quality control of mud maturation. The development of green microbial mats or biofilms on mature thermal mud is a peculiarity of Euganean peloids, wherein optimal mud maturation, in terms of bioglea or biofilm, takes place in the temperature range 30–42°C. The study revealed a stable microbial community showing a general phyla composition comparable to those found in similar conditions in natural springs around the world, but the Cyanobacterial composition of Euganean thermal muds is peculiar and unique. According to Baldovin et al. (2020), the evaluation of hygiene aspects of thermal muds used in pelotherapy continues to be neglected. Baldovin et al. (2020) evaluated the microbiological hygiene quality of thermal muds, before and after maturation, used in a significant number of spas from the Euganean Thermal District. Total coliforms, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, and sulfite-reducing clostridia have been identified and quantified (CFU/g). The authors recommended the compulsory pasteurization of peloids just before every treatment using thermal water at a temperature of 60°C or above, in order to ensure hygienic quality.

In Europe, for cosmetics peloids, qualitative and quantitative guidelines exist that guarantee their sanitary safety against pathogenic microorganisms (European Standard EN ISO 17516:2014 Cosmetics-Microbiology-Microbiological Limits); no equivalent exists for therapeutic or medical peloids, which are used in balneological treatments of rheumatic disabilities. In the case of peloids, it is important to use medical and cosmetics peloids which are free of pathogens, as well as bactericidal peloids and bactericidal ointments (Gomes et al. 2020). The International Standard ISO930:2012 indicates how to assess the overall antimicrobial protection of cosmetics clay-based products.

In pelotherapy, in order to be bioavailable, any potentially active substances presumably have to be present in the peloid liquid phase. Experimental work has been done on the production of a tailored peloid or a 'designed and engineered' peloid, based on a secondary peloid (solid and liquid phases obtained from different sources), in order to obtain a potential peloid (Gomes et al., 2018, 2019b, 2020). (By definition, a real peloid is one for which therapeutic or cosmetics properties are recognized medically.) The potential peloid has a very simple composition capable of being prepared chemically and microbiologically and controlled in aseptic conditions. To this end, samples of Kaolin-A130, previously refined (to grainsizes of <45 μm and <10 μm, the latter utilized for ointment) and sterilized using an oven and a two-stage heating procedure (105°C/12 h and 200°C/30 min), were blended in a 1:1 weight ratio (w/w) with São Pedro do Sul Thermal Water (SPSTW) used ~2 h after collection in a sterile bottle at the spring source and analyzed microbiologically.

The resultant potential peloid was prepared in aseptic conditions using a laminar flow cabinet. Still inside the laminar flow chamber the resulting pastes were placed in appropriate sterile bags for pressure pasteurization and sealed. Next they were placed in the X-brand homogenizer for 3 min and submitted to non-thermal pasteurization in a high-pressure processing unit (Hiperbaric, Burgos, Spain, model 55 L) at 600 MPa/18°C for 15 min. Microbiological analyses were carried out on the 'potential peloid' after processing and after various periods of storage in order to assess its safety (Gomes et al., 2018, 2019b).

The high-pressure processing method is a cold pasteurization method that is currently used for food preservation.

Bactericidal Peloid and Bactericidal Ointment

Experience has shown that some natural clays containing reduced metals could exhibit bacteriostatic and bactericidal properties. Dozens of scientific papers can be found in the literature which have investigated and described the mechanisms of the action of the so-called 'natural killer clays,' which might well provide an answer to 'superbug' infections or disease-causing microorganisms. 'Superbugs' are pathogens or disease-causing microorganisms resistant to wide ranges of antibiotics (Caflisch et al., 2018; Gomes et al., 2020; Otto & Haydel, 2013; Otto et al., 2014; Santos et al., 2011; Stucki & Kostka, 2006; Wang et al., 2017; Williams, 2017, 2019; Williams & Haydel, 2010; Williams et al., 2004, 2008, 2009). The bactericidal activity of the natural clay is performed only when the clay is wet, and reduced transition metals (most commonly Fe^{2+}) are part of its composition. The mechanisms of the clay-adsorbed cytotoxic metals, followed by their oxidation to generate hydroxyl radicals responsible for the permeation of cell bacteria and the damage to bacteria cytoplasm proteins and DNA, have been established (Morrison et al., 2016; Londoño et al., 2017; Caflisch et al., 2018; Williams 2019). Natural, non-bactericidal clay may be transformed into bactericidal clay, as described by Gomes et al. (2020) and Awad et al. (2021).

Using the combined methodology mentioned above, Gomes et al. (2019b, 2020) produced a bactericidal peloid and bactericidal ointment, both free of pathogens, their formulations being based on blends of Kaolin A-130 (a commercial Portuguese kaolin of high whiteness and grain sizes of <45 μm and <10 μm, which was previously analyzed chemically and sterilized by heating in an oven at 200°C for 30 min), and on bicarbonate of sodium sulfurous medicinal natural mineral water (SPSTW) from the Portuguese São Pedro do Sul thermal spa. To achieve the required bactericidal activity, an acid solution of $FeSO_4$ was added to the blend that was then pasteurized by high hydrostatic-pressure processing. To test peloid and ointment bactericidal activity, the following three bacteria strains were used: *Pseudomonas aeruginosa* 67p, *Staphylococcus aureus* ATCC 6538, and *Escherichia coli* ATCC 25922. Several other functional additives, natural or synthetic, e.g. marine microalgae and cyanobacteria bearing high concentrations of biologically active substances (Mourelle et al., 2017), could be introduced into formulations of both therapeutic and cosmetic peloids.

The flow sheet of the high-pressure processing methodology adopted to achieve a pasteurized 'designed and engineered' peloid prepared by blending Kaolin A-130 (grainsizes of <45 μm or <10 μm) with thermal mineral medicinal water from São Pedro do Sul is illustrated in Fig. 2. Firstly, the Kaolin A-130 was sterilized at 200°C using the oven, and then the kaolin/water paste was pasteurized using the high-pressure method.

Incorporation in the potential peloid of functional additives, natural or synthetic, could make it more active, developing bactericidal properties by adding a reduced metal-bearing additive, e.g. a solution of $FeSO_4$. Such properties are potentially good for the treatment of skin infections, e.g. infected wounds, common in the feet and legs of diabetic people, and to treat other skin infections. If necessary, an appropriate preservative could be added to guarantee peloid microbiological stability/integrity.

A general flow sheet of the recommended methodology to be used in the preparation of safe 'designed and engineered' peloids is illustrated schematically in Fig. 3. Due to their simple composition, controlled processing, and evaluation, 'designed and engineered' peloids of both medical and cosmetic typologies can be submitted periodically to both chemical composition control (comprising the identification and quantification of inorganic or mineral and of organic constituents) and sanitary control comprising the identification and quantification of pathogenic microorganisms.

Kaolin A-130 was selected for this task because of its white color and fine grain size, and because it was composed essentially of a structurally disordered kaolinite (characterized by greater SSA and greater net negative electrical charge than a structurally well-ordered kaolinite). More Fe^{2+} ions would be fixed electrostatically on the surfaces of kaolinite particles and available for exchange.

The enhanced antimicrobial activity of a pyro-fabricated, silver-kaolinite nanocomposite (Ag-Kao nanocomposite), obtained by heating at 400°C mixtures of kaolinites differing in structural order with an acid solution of $AgNO_3$, was demonstrated experimentally by Awad et al. (2021). Naturally, because the nanocomposite has a larger SSA and electrical charge values, that antimicrobial activity was found to be enhanced in the less structurally ordered kaolinites, than in the structurally well-ordered kaolinites.

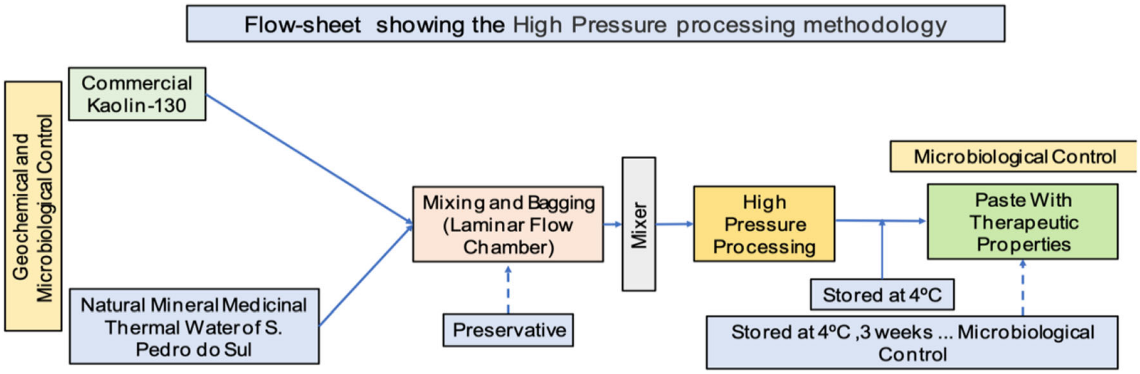

Fig. 2. Flow-sheet showing the high-pressure processing methodology employed to achieve a pasteurized 'designed and engineered' peloid prepared by blending Kaolin A-130 (grain size <45 μm) with sodium bicarbonate and sulfurous natural mineral water (SPSTW) from São Pedro do Sul thermal spa (Gomes et al. 2018)

Podoconiosis

Exceptionally, clay can be the cause of disease. In some environments and conditions, some clays and clay minerals may cause disease in humans, as is the case with podoconiosis, a term derived from the Greek words 'podos' (foot) and 'konos' (soil).

In the literature, there are also references to diseases, the etiology of which has been attributed to soil clay, such as: Mseleni Joint's, Kashin-Beck's (KB), and Keshan´s (K) diseases. According to Finkelman (2019), many studies have recognized the relationship between KB and K diseases and selenium-deficient soils (Tan et al., 2002) but few studies discuss the role of the soil-clay content, type, or chemistry (Lv et al., 2014).

Podoconiosis is a disease the etiology of which has been attributed to tropical, high-altitude, volcanic red clayey soils,

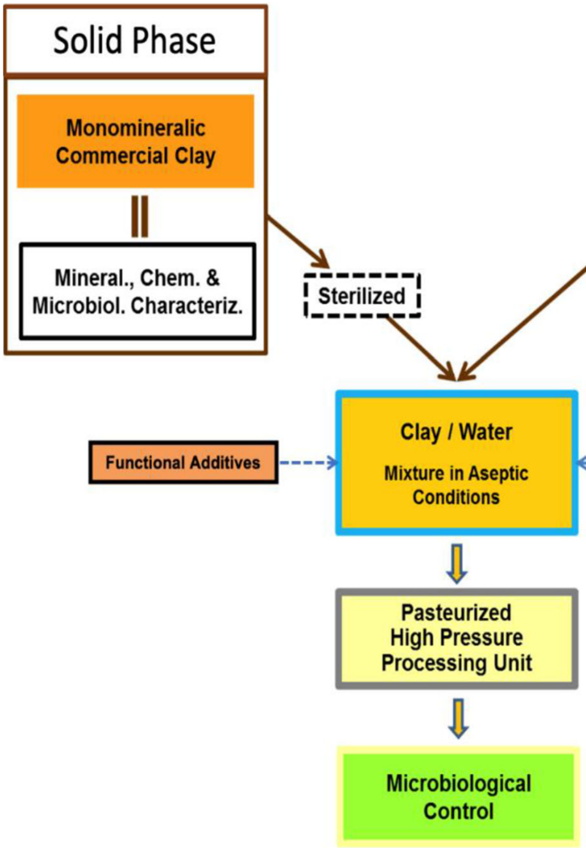

Fig. 3. Flow-sheet showing the general methodology adopted for the preparation of safe 'designed and engineered' peloids (Gomes et al., 2019a, b; adapted from Gomes et al., 2015)

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and is one of the few diseases that could potentially be eliminated within a single generation, because it is limited to people who live and work barefoot (Buck et al., 2016; Chandler et al., 2021; Crivelli, 1986; Davey et al., 2007; Davies, 2008, 2010; Davies & Mundlano, 2010; Deribe 2018; Deribe et al., 2015a, 2015b, 2015c, 2017; Feleke, 2017; Gomes et al., 2021a; Jones et al., 2015; Lyles, 2018; Molla et al., 2014; Nordberg & Cherian, 2005; Price, 1976, 1977, 1988; Price & Bailey, 1984; Tsegay et al., 2016).

The global distribution of the disease remains largely unknown. Podoconiosis was said to exist or be endemic in 32 countries, 18 from Africa, three from Asia, and 11 from Latin America (Deribe et al., 2018). The greatest reported prevalence was in Africa (8.08% in Cameroon, 7.45% in Ethiopia, 4.52% in Uganda, 3.87% in Kenya, and 2.51% in Tanzania). In India, a single prevalence of 0.21% was recorded from Manipur, Mizoram, and Rajasthan states. None of the Latin American countries reported prevalence data. Based on data collected by the present authors, podoconiosis is suggested to be more widespread in Africa than elsewhere though this could be related to the fact that most podoconiosis epidemiological research has been focused on the African continent. The distribution of podoconiosis is limited to tropical and subtropical areas where red clay soils are formed from basaltic rocks weathering under specific environmental circumstances, including altitude (1000–1500 m above sea level), high seasonal rainfall (1000–10,500 mm annually), and a mean annual land surface temperature of 19–21°C.

In endemic areas, podoconiosis is a disabling condition and often an occupational-health issue; it poses a considerable public health problem. In local communities, podoconiosis is often referred to as 'mossy foot disease.'

In 2011, the World Health Organization (WHO) designated podoconiosis as one of the 20 neglected tropical diseases, with others such as Buruli ulcer, leishmanisis, cysticericosis, chagas disease, leprosy, fascioliasis, and lymphatic filariasis (elephantiasis). Podoconiosis is caused by submicron and nanoparticles of clay penetrating the skin of feet and lower limbs, with local lymphatics becoming obstructed. Those particles enter into the blood through abrasions in the feet and affect the cells of the immune system, the pathogenicity depending on particles enriched in Fe, Al, and Ti, from basic and acid volcanic rocks, alkali basalts, and tuffs. Using statistical analysis, a positive correlation between smectite, quartz, and mica and the prevalence of podoconiosis in northern Ethiopia was demonstrated by Molla et al. (2014).

The bioreactivity of red clays from basalt weathering in the volcanic island of Madeira, Portugal, was assayed by Jones et al. (2015) and shown to cause podoconiosis. These clays are composed mostly of kaolinite and iron (oxyhydr)oxides. The reaction of the red clays against DNA and different types of human cells were assessed by Jones et al. (2015) who found that the red clays damaged DNA, attacked immune cells, and lysed human blood cells (haemolysis). Samples of these red clays which have been collected recently from intensively farmed red clayey soils called 'nateiros' and being the result of basalt and tuff weathering were found to consist of halloysite nano-spherules and quasi-amorphous iron hydroxides.

The report 'Environmental Health Criteria 231' issued in 2005 by the WHO assessed the risks to human health posed by environmental exposure (general and occupational) to clays and clay minerals such as bentonite, kaolin, and fibrous clays. The conclusion indicated a very low toxic risk to humans for the types of clays listed.

The pneumoconiosis known as Kaolinosis could be developed after long-term exposure to fine and ultrafine kaolin particles present in the air near mining works, and not due specifically to kaolinite but rather to quartz associated with it in clayey soils.

CONCLUSIONS AND PERSPECTIVES

Among all geologic resources, clay has the most diverse applications; developments in geology and materials science have provided new insights into the field of clay applications. Today, when nanotechnology is the hallmark of the scientific world, the so-called nanoclays are fundamental raw materials for several essential technological applications such as catalysis, food packaging, animal feed, textiles, medical devices, medicines, and drug carrying.

Interest in clays for healthcare, shown synoptically in the present paper, is due in particular to clay properties such as biocompatibility, nanometric size, adsorption and absorption capacities, low toxicity for oral and topical administrations, easy availability, and low cost. Note especially the increasing interest and research into the use of clay minerals for therapeutic and cosmetic purposes, especially as agents able to carry specific and functional drugs either adsorbed or absorbed in order to be delivered to target sites in the human body and released in a controlled manner, and as promising agents in regenerative medicine.

Peloid *stricto sensu* and its derivative 'designed and engineered' peloid are, in general, clay-water mixtures, either more fluid (facial mask), or less fluid (peloid pack and peloid compress). Emphasis has been placed here on the healing properties of both bactericidal peloid and bactericidal ointment, the potential benefits of which require clinical evaluation.

The present authors, based on previous research, have demonstrated the opportunity to transform a non-bactericidal clay into a bactericidal one, characterized by chemical and physical properties appropriate for therapeutic and dermocosmetics applications, e.g. in treating infectious skin wounds. Similar modifications can be achieved by adding solutions bearing reduced metals to clay-water systems used in the preparation of extemporaneous peloids, or, more precisely, of bactericidal 'designed and engineered' peloids and bactericidal ointments. The bactericidal character has been found in some natural clays and zeolites which include reduced metals in their compositions. From an applied point of view, and based on experimental data, the present authors have demonstrated the preference for modified clay-water systems of very simple and controlled composition, not showing any

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bactericidal activity, with clay and water being both support and vehicle to outsider bactericidal agents. Preference is also given to clays and clay minerals and to water for their potential or real medicinal assets and easy sterilization, e.g. kaolin, bentonite, or sepiolite for the clay component, and natural mineral water or spring water for the water component. Clinical assays and assessment are now needed.

Constraints, both chemical and microbiological, on the use of clay-based products for therapeutic and cosmetics topical applications are imposed generally by sanitary regulations, and some solutions have been proposed to control and reduce such restrictions. It has become clear from the available literature on both positive and negative interactions of clays and clay minerals with human health that more clinical studies, including tests 'in vivo' on people, are required to confirm or deny such interactions. This is the case for other subjects within the scientific field known as 'medical geology'; good fundamental and applied studies have been carried out involving geology, mineralogy, geochemistry, physics, etc., but a decisive medical contribution has not yet been achieved.

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Declarations

Conflict of Interest

The authors declare that they have no conflict of interest.

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