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PHYSICO-CHEMICAL PROPERTIES OF MONTMORILLONITE CLAYS AND THEIR APPLICATION IN CLINICAL PRACTICE (REVIEW)

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Abstract
The review is devoted to the medical application of montmorillonite clay minerals.
Properties and mechanisms of action of enterosorbents. The properties of the enterosorbents include an absorption capacity and active surface. The mechanisms of action include the sorption of toxins in the gastrointestinal tract, the contact effect on the mucosa, enhancing the release of toxins in the gastrointestinal tract, increasing the metabolism and excretion of toxins.
Physico-chemical properties of montmorillonite. Montmorillonite is a layered silicate from the smectite group, with the structure of 2:1. Its specific area is 173 m^2/g and sorption capacity is 370 mg/g.
The application of montmorillonite clays in medicine. Smectites are used as excipients, active substances or dispersants.
Oral effects of smectite. The smectite based enterosorbents have antacid, mucocytoprotective, antidiarrheal effects, a high sorption activity against bacterial and viral particles.
Analysis of the clinical use of the smectite based enterosorbents. Diosmectite has a high strength of recommendations and security (class B). The analysis is based on the results of the randomized clinical trials. According to different authors, from 22 to 84% of European doctors prescribe smectite for acute diarrhoea. Smectite reduces the duration of diarrhea by 22-42%, significantly reducing the number of bowel movements in comparison with placebo ($p<0.001$). The drug is well tolerated and has no side effects.
Key words: montmorillonite; smectite; medical clays; layered aluminosilicates; enterosorbents.

Introduction

Efferent therapy as a method of elimination of toxic products from the body's environment is gaining popularity in various branches of clinical medicine. Among all the methods of efferent therapy, this method of non-invasive detoxification as enterosorption attracts close attention, which, with adequate use, allows achieving a local and systemic positive effect.

Removal of compounds that negatively affect the body, such as allergens, active peroxides, viruses, toxins, inflammatory mediators, as well as preventing their movement into the systemic bloodstream, stimulates the mechanisms of resistance of the organism, prevents the development of excessive inflammatory reactions, improves metabolism [1, 2].

Adsorption is a process that occurs on the phase separation when a gas or liquid substance accumulates on the surface of a solid or liquid (adsorbent), forming a molecular or atomic film (adsorbate) [3]. Typically, the adsorbent has a fixed total absorption, where a particular solute is replaced by another, for example, in ion exchange processes. When the adsorbent is in contact with a liquid containing the substance to be absorbed, adsorption occurs until equilibrium is reached or when the surface of the adsorbent is saturated with adsorbate [4].

The adsorption process can be divided into two main types, namely the physical and the chemical, which are sometimes called physiosorption and chemisorption, respectively. The difference between the two types of adsorption is that during physical adsorption, the adsorbate adheres to the surface through weak intermolecular interactions, such as van der Waals forces, hydrophobicity, hydrogen bonds, polarity, static interactions, and dipole-dipole interactions [5]. On the other hand, during chemisorption, molecules attach to the surface, forming a chemical bond through electronic exchange [6].

Properties and mechanisms of action of enterosorbents

Enterosorbents have a number of basic characteristics, namely: sorption capacity – the amount of a substance that can bind a sorbent per unit of its mass (mg/g); Active surface – the total area of the adsorbing surface per unit mass (m^2/g); The sorbent's ability to bind various sorbate molecules of different mass and size, including bacterial agents [7, 8].

As a rule, the more sorption surface of the sorbent, the higher its sorption capacity [9, 10]. However, it should be noted that the sorption capacity of the sorbent, determined "in vitro", can significantly differ from that in clinical practice. In this respect, a study conducted by P.L. Shcherbakov and V.A. Petukhov in 2005 is indicative. When analyzing the sorption activity of enterosorbents with respect to the endotoxin Salmonella abortus, the maximum absorption rate was recorded in smectite dioctahedral (Smecta®) having a lower sorption surface (100 m^2/g) than methyl silicic acid hydrogel (150 m^2/g), known under the trade name Enterosgel®, which showed a lower rate of endotoxin sorption [11]. This allows us to reflect on the compliance of technical laboratory characteristics of sorbents and their sorption efficiency with respect to biological objects. In addition, in some works it is pointed out that in some cases clay sorbents with a lower active area show a much more pronounced sorption capacity. This applies mainly to montmorillonite, which has an active area of 173 m^2/g and a sorption capacity of 370 mg/g, which is much higher than that of all native clays under study [12].

The main mechanisms of action of agents used for enterosorption include the following four groups. The first group of mechanisms concerns direct interaction and sorption in the lumen of the gastrointestinal tract of toxic products, exo- and endotoxins, pathogenic and conditionally pathogenic microorganisms, possible allergens. This applies to xenobiotics and metabolites both trapped in the lumen of the gastrointestinal tract from the outside, and formed in the lumen of the intestine. The second group refers to the contact effect on the structures of the gastrointestinal tract, including the effect on the enzymatic composition of the gastrointestinal mucosa, the content of various substances having biological activity in the intestinal tissues and, as a consequence, a change in the functional state of the gastrointestinal tract. The third group is the stimulation of the release of endotoxins from the systemic blood stream and internal media into the lumen of the gastrointestinal tract by direct diffusion from the blood and/or to a greater extent with digestive juices. The fourth group of mechanisms includes indirectly enhancing the exchange and excretion of toxins by detoxifying organs, as well as fixing and transferring biologically active substances, such as enzymes and bile acids to the surface of enterosorbent [7, 13, 14, 15].

Physico-chemical properties of montmorillonite

To date, a lot of interest is caused by enterosorbents based on clay minerals belonging to the subclass of smectites [16, 17, 18, 19, 20, 21, 22]. Almost 90% of world production of smectites is concentrated in 22 countries, including Australia, Mexico, Russia, South Africa, USA [23].

Enteric sorbents based on smectite clays are characterized by the ability to exert a soft effect on the mucous barrier, not to bind cells of the normal microflora of the gastrointestinal tract and physiologically valuable nutrients, to not disturb the secretion processes, to improve rheological properties of mucus and immunity parameters [1, 24, 25].

Montmorillonite refers to layered clay minerals of the smectite group with a high content of SiO_2 and Al_2O_3 with a 2:1 structure. This means that the unit cell of this clay mineral consists of three sheets of crystal lattices of a tetrahedral and octahedral structure. The crystal lattice includes an aluminum-oxygen and aluminum-hydroxyl-octahedral sheet sandwiched between two silicon-oxygen tetrahedral sheets (Fig. 1). The structure of the triple sheet is composed of layers connected by van der Waals forces [26, 27, 28, 29, 31]. The thickness of the layer is about 1 nm, and the transverse dimensions of these layers vary from 100 nm to 1000 nm [20, 30, 31, 32, 33]. The unit cell of montmorillonite includes four octahedral sites and eight tetrahedral sites, that is, montmorillonite belongs to the subclass of dioctahedral smectites. This is due to the fact that trivalent cations prevail in its octahedral layer, such as aluminum and iron cations [34, 35, 36, 37, 38]. The ideal theoretical formula for montmorillonite is as follows: $(M_y^+ \times nH_2O)(Al_{2-y}^3 Mg_y^{2+})Si_4^{4+}O_{10}(OH)_2$, where M^+ refers to a monovalent cation in the interlayer space, but in reality the composition of montmorillonite differs from the theoretical formula due to the substitution of a number of cations for others [33, 39].

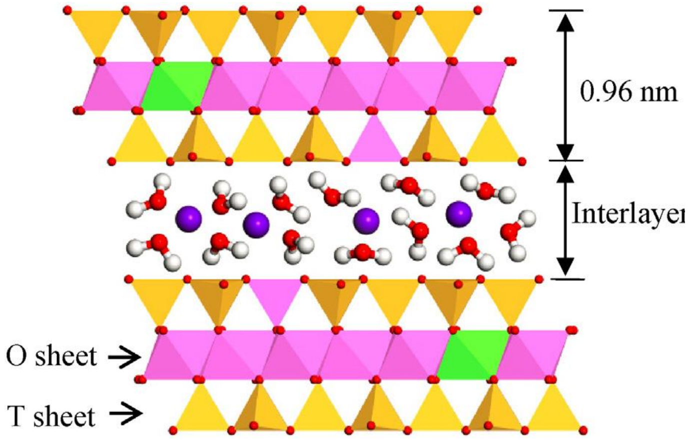

Fig. 1. Model of the structure of montmorillonite layers [32]

On the external surface of montmorillonite there are both interlayer and ionized hydroxyl centers [40]. Cations in the tetrahedral sheet are usually Si^{4+} and Al^{3+}, in the octahedral sheet – Al^{3+}, Fe^{3+}, Mg^{2+}. Because of the isomorphous substitution of cations in both tetrahedral (Si^{4+}) and/or octahedral (Al^{3+}, Fe^{3+}, Mg^{2+}) sheets by lower valence cations, the layered structure acquires a constant common negative charge, which is balanced by cation exchange within the interlayer space [31, 33, 41]. Negative charge contributes to the ability of the clay to adsorb positively charged ions. In addition, the adsorption characteristics of clays are due to their large pore size and surface area. These factors affect the physical properties of montmorillonite, such as the sorption surface and the sorption capacity [42, 43, 44]. The phenomena that occur on the surfaces of the clay give them high flexibility in adsorption processes. The nature of the surface includes the structure, ion exchange capacity, specific surface area, mechanical and chemical stability, water retention and surface reactivity, which affects the physical and chemical properties of clay minerals [45, 46]. As a rule, clays have replaceable ions on their surface [45]. The inter-pack space of montmorillonite contains exchange cations of alkali and alkaline-earth metals and water molecules. This characteristic leads to the fact that clays play a decisive role in the environment, being natural adsorbents of pollutants. Cation exchange occurs easily, without affecting the structure of the clay mineral [47].

Depending on the prevalence of the exchange cation in the crystal lattice structure: Montmorillonites can be of sodium or calcium type [37]. Calcium montmorillonite is the most common of smectites and is found in many geographical places of the world. Sodium montmorillonite is relatively rare compared to calcium montmorillonite, and it swells more in water than calcium montmorillonite [48, 49]. The presence of an exchange cation (sodium, calcium) increases the distance between the layers of montmorillonite structures, and as a consequence, ensures the penetration of water molecules between them [50].

Montmorillonite possesses high sorption properties due to its structural characteristics. The main characteristics of this material are high internal surface area, high adsorption capacity, high cation exchange capacity, swelling, low hydraulic conductivity and low toxicity [42, 51, 52, 53, 54].

Usually, these clay materials are used as natural materials, since they are not subjected to a chemical change. Nevertheless, chemical modification can improve the adsorption capacity of clay, which leads to its wide use in new technologies [44, 55, 56].

Chemical treatment of clay can change its structure, texture and / or other properties [57]. Indeed, clay minerals are usually classified into natural clays, clays subjected to activation (alkaline or acid treatment) and organic clays (treatment with organic substances) [58].

Alkaline activation is usually carried out by treatment with sodium carbonate (soda). Activation of 2-4% of soda is traditionally used to treat low-quality smectites in industry [59].

Acidic activation of smectite clays with the help of hydrochloric and sulfuric acids leads to a change in their composition, surface area and porosity, and also to an increase in their absorbing properties [60, 61, 62]. In addition, acid treatment removes calcium ions from the surfaces and edge regions of the layers, which increases the total negative charge [63, 64, 65].

Organic smectite clays are obtained by modifying clays with quaternary ammonium cations by cation exchange [49]. During this procedure, the hydrated cations (Na^{+}, K^{+}, Ca^{2+}, Mg^{2+}) that neutralize the excess negative charge arising from isomorphous substitution in silicon tetrahedra and/or aluminum octahedra are replaced by cations of quaternary ammonium in the interlayer space [66]. Inorganic cations are gradually replaced by organic cations. Thus, the surface of organic smectite changes from highly hydrophilic to hydrophobic [67, 68].

The administration of montmorillonite clays in medicine

Montmorillonite clays due to their properties are widely used in medicine and the pharmaceutical industry. For this reason, they are often called medical clays [17]. Smectites are commonly used in the pharmaceutical industry as excipients, active substances or dispersants that perform technological functions [48, 69, 70]. New fillers with very specific goals are added to most new medicines. Such targets are varied to include a decrease or increase in dissolution rate, drug release delay, drug release targeting (biopharmaceutical targets), prevention or reduction of side effects (pharmacological targets), taste masking or stability improvement (technological objectives) [70, 71, 72].

Montmorillonite has attracted much attention due to its ability to allocate drugs in a controlled way, its mucoadhesives and strong detoxification effect, which ultimately leads to high drug efficiency [26, 29, 73]. Moreover, the use of montmorillonite corrects gastrointestinal disorders, one of the most common side effects of cancer chemotherapy [27, 70, 74, 75].

Clay minerals are also used as active ingredients in cosmetic products, such as face masks, due to the high content of absorbent substances that contribute to the removal of fats and toxins from the skin surface [71]. Therefore, they are recommended for inflammatory processes such as furuncles, acne and ulcers, as antiperspirants, to make the skin opaque, remove gloss and pigment spots from the skin surface [71, 76].

In addition, medical clays used in creams, powders or emulsions contribute to an increase in the amount of collagen fibers in the skin, suggesting that the protective mechanism of smectite appears to be mediated by a combination of allergen uptake and improved skin barrier function, and by providing a physical barrier Against ultraviolet radiation [77].

Oral effects of smectite

Oral application of clays in the treatment of certain diseases is based on the ability of clay and clay minerals to sorb, retain and eliminate xenobiotics, microorganisms and toxic products of their activity, toxic digestive products, gases, food allergens. A number of studies have shown the positive effect of preparations based on clay minerals in the treatment of a number of pathological conditions, mainly in diseases of the gastrointestinal tract [78]. The use of clay as a medicine, and also as a food additive has an ancient history. Oral application of clays ("geophagia") has been practiced since antiquity in all parts of the world. Among the whole variety of clay minerals, in ancient times primitive tribes mainly used clays with a high content of montmorillonite to prevent stomach pain, digestive disorders, burn treatment, reduce gastric acidity, improve taste qualities [79, 80]. To this day in many areas of the world, clay minerals are used for food. There are several reasons for geophagy: 1. detoxification, or at least improvement in the taste of foods containing unwanted components; 2. alleviation of gastrointestinal disorders such as diarrhea; 3. Preparation of mineral additives, in particular iron and calcium; 4. as an antacid to remove excess acidity in the digestive tract. These reasons make geophagy culturally acceptable in the modern world [81]. In general, of all clays, smectites (including montmorillonite) are considered more reactive in the gastrointestinal tract [82].

Smectites, including montmorillonite after oral ingestion has an antacid, antidiarrhoeal, cytoprotective against the mucosa of the gastrointestinal tract properties.

The increased acidity in the stomach resulting from excessive formation of hydrochloric acid by parietal cells of the gastric fundal glands can be effectively reduced by oral use of non-systemic antacids, such as montmorillonite-based enterosorbents. Clay minerals have an antacid effect through two mechanisms: (a) the direct neutralization of hydrochloric acid in the stomach and (b) the adsorption of H + ions on the surface of the enterosorbent. The antacid effect of montmorillonite clays is due to a second mechanism, that is, the sorption of hydrogen cations on the surface, as well as in the interlayer space of the mineral. The main centers of interaction of montmorillonite and hydrogen cations are the structural cations of the octahedral and tetrahedral layers (Mg^{2+}, Al^{3+}), as well as the interlayer space and cations located in it [83, 84].

Clays from the smectite group, when administered orally, have a stabilizing effect on the barrier functions of the gastrointestinal mucosa, interacting directly with mucus elements. Thus, clay minerals improve the protection of the mucosa from aggressive factors acting on the mucosa of the gastrointestinal tract [85, 86, 87].

When interacting with mucus in the gastrointestinal tract, smectite forms a protective film on the mucosal surface, which reduces the aggressive action of the stomach environment. In addition, it sorbs gases, toxins, bacteria and viruses. The mechanism of protective action is to increase the viscosity of mucus and inhibit the degradation of glycoproteins that make up its composition. Smectite reduces the destruction of mucus by bacteria and disruption of the integrity of membranes of enterocytes, which causes normalization of the water-electrolyte balance and absorption of nutrients [88, 89]. At the moment in Russia smectite is the only enterosorbent with proven cytoprotective properties [11].

Diarrhea is an acute or chronic pathological condition in which there is increased fluid formation in the lumen of the gastrointestinal tract and its rapid evacuation by natural means. This is manifested by a rapid liquid stool, abdominal pain, increased gas production. Diarrhea can be caused by bacterial infection, intoxication, inadequate intestinal absorption, allergy, etc. In this regard, smectite is widely used to stop diarrhea, sorbing excess fluid, gases, bacterial toxins in the lumen of the gastrointestinal tract, contributing to the reduction of inflammation in the wall of the small and large intestine [25, 90, 91].

In vitro conditions, smectite and psyllium have been found to possess the highest sorptive capacity for *S.enteritidis* and *E.coli*. The smectite results were better not only in the number of adsorbed bacterial cells, but also in the number of cells remaining in the solution after removal of the sorbent [92]. In the experiment, the high sorption ability of smectite was also shown for some other gram-positive bacteria (*V.cholerae*, *C.jejuni*, *C.difficile*, *Shigella sonnei*), their toxins and metabolites, and also for rotavirus. Smectite is able to fix on its surface and eliminate up to 90% of viral particles [11, 93, 94, 95].

In addition, enterosorbents have the ability to the so-called distant action, which manifests itself in the change of various biochemical parameters in tissues and organs, far removed from the gastrointestinal tract. This mainly relates to changes in the functional state of the liver, reduction of the total cholesterol in the blood, the appearance of an immunomodulatory effect associated with a decrease in antigenic effect due to improved proteolysis in the food lump [14].

It should be especially noted that enterosorbents are not absorbed in the gastrointestinal tract, and, as a consequence, do not have a resorptive effect. This property is fundamental for enterosorbents and is presented with the main requirement on a par with the absence of toxicity in the search for new substances for enterosorbents.

Analysis of the clinical administration of smectite based enterosorbents

Based on data from evidence-based medicine, it can be said with certainty that sorption therapy with smectite-based drugs is widely used in clinical medicine to treat diseases associated with endogenous intoxication syndrome in both children and adults, including pregnant women. It should be noted that among all enterosorbents in acute gastroenteritis in children and adults, only dioctahedral smectite has a high degree of evidence and safety (class B) [96, 97, 98].

Trust in enterosorbents based on smectite dioctahedral is extremely high among doctors. This is true both for developing countries and for developed countries. So Szajewska (2000) points out that 22% of doctors in European countries use smectite to treat gastroenteritis in children as an adjuvant therapy. According to Uhlen (2004), the use of smectite by French pediatricians in private medicine reaches 84%. In clinics in Prague, about 46% of children with acute diarrhea received smectite (Kudlova, 2010). Hou (2013), based on the analysis of appointment sheets in 20 hospitals in two provinces of China, notes that almost two thirds of adults suffering from acute infectious diarrhea have been prescribed diosmectitis [99].

As a result of a multicenter, randomized, double-blind, placebo-controlled study, dioctahedral smectite has a high oral efficacy for the treatment of acute diarrhea in adults compared to the placebo group, which was manifested by a reduction in the timing of recovery. In this case the drug was well tolerated, and the patients did not notice any negative side effects [100].

When testing the safety and tolerability of NovaSil® enterosorbent, which contains dioctahedral smectite, which was used at a high risk of aflatoxicosis in Ghana, no side effects of the drug were found. During the study, 0.5% reported nausea, diarrhea, heartburn, and dizziness with both NovaSil® and placebo, indicating high safety when using dioctahedral smectite [19, 101, 102].

Diosmectit is one of the most effective and safe antidiarrheal agents that can be used in children as an adjunctive therapy to oral rehydration to reduce the timing of diarrhea and reduce its volume. This was shown in two parallel, double-blind clinical trials with the participation of 602 children aged 1 to 36 months with acute diarrhea and dehydration symptoms, which were conducted in Malaysia Peru. Children received diosmectite at a dose of 6 g per day between 1 and 12 months and 12 g per day between the ages of 13 and 36 months for 3 days, with a decrease in dose twice in the following days until relief of signs of diarrhea or placebo. The results were presented separately for two groups of the population. In Peru, in the diosmetic group compared to the placebo group, the total amount of stool at the 72nd hour of treatment was reduced (102.0±65.5 g/kg versus 118.8±92.5 g/kg, p=0.032) and more Short duration of diarrhea (68.17 h against 118.92 h, p=0.001). Positive effect of diosmectite was exposed to both rotavirus-positive and rotavirus-negative children. In Malaysia, the 72 hour mass was also significantly lower in the group receiving diosmectitis than in the placebo group (87.9±81.2 g/kg versus 90.7±94.0 g/kg, p=0.007). The duration of diarrhea was significantly reduced in children receiving diosmectitis than in the placebo group (25.1 h versus 32.6 h, p=0.001). However, in this case, the positive effect of treatment with diosmectitis was observed only in rotavirus-negative children [103].

A later, open-label, randomized clinical trial in India found that dioctahedral smectite shortens the duration of diarrhea. In this study, 117 children aged 2 to 5 years with acute diarrhea were prescribed diosmectitis in a dose of 1.5 g three times a day for 5 days or placebo. Children who received smectite recovered more quickly than in the placebo group. This was manifested by a decrease in the resolution time of diarrhea (64.34±14.86 h against 82.37±21.43 h, $p<0.001$). Thus, the results of numerous studies confirmed that smectite clay enterosorbents as a supplement to the standard rehydration therapy for acute diarrhea have high efficacy, which is indicated by a reduction in the timing of diarrhea resolution, a decrease in stool volumes, and a reduction in recovery time [104].

As a combined meta-analysis of nine randomized controlled trials has shown, smectite in children reduces the duration of diarrhea by an average of 23 hours, and, moreover, significantly reduces the total number of defecations in comparison with placebo. Treatment was accompanied by an increased likelihood of recovery on day 3, in addition, the use of smectite significantly reduces the likelihood of diarrhea lasting more than 7 days. In all studies of side effects with short-term therapy with dioctahedral smectite was not found [96].

Conclusion

Thus, evidence of the effectiveness of enterosorbents based on smectite clays is very wide in both developed and developing countries, when used in inpatient and outpatient settings. Mechanisms involved in the antidiarrheal effect include increased colonic mucin secretion and modulation of cytokine production by mucosal cells, as well as effects on intestinal permeability and secretion of electrolytes. In addition, montmorillonite has a mucocytoprotective effect, affects the production of enzymes and cytokines by cells of the gastrointestinal tract, has a variety of long-range effects, has a pronounced detoxification effect.

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References

1. Golubev N.N., Maev I.V. Samsonov A.A. Aspects of the clinical use of enterosorbent Neosmectin. *Diseases of the digestive system*. 2008. № 2 (10): 62-65. [Full text]

2. Uchaykin V.F., Novokshonov A.A., Sokolova N.V. Enterosorption is an effective method of etiopathogenetic therapy of acute intestinal infections. *Infant Infections*. 2005. № 3: 39-43. [eLIBRARY][Full text]

3. Oremusovà J. *Manual for laboratory practice in physical chemistry for students of pharmacy*. (Department of Physical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, in Slovak, 2007). [Full text]

4. Kalibantonga P.D. Adsorption of Heavy Metals from Solution by South African Industrial Clay. *A thesis submitted at Tshwane University of Technology*. 2004.

5. Dawood S., Sen T. Review on dye removal from its aqueous solution into alternative cost effective and non-conventional adsorbents. *J. Chem. ProcessEng*. 2014. 1: 104. [Full text]

6. Artioli Y. Adsorption. In: Erik Sven, Brian F. (Eds.). *Encyclopedia of Ecology. Academic Press*. (Oxford, 2008): 60-65. [PubMed]

7. Panfilova V.N., Taranushenko T.E. Application of enterosorbents in clinical practice. *Pediatric Pharmacology*. 2012. V.9, №6: 34-39. [eLIBRARY][Full text]

8. Buhanov V.D., Vesentsev A.I., Naumenko L.I., Sokolovsky P.V., Pankova O.N. Influence of the enterosorbent on quality of eggs. *Research result: pharmacology and clinical pharmacology*. 2016. Vol. 2, №2: 107-112. [eLIBRARY][Full text]

9. Worch E. *Adsorption Technology in Water Treatment: Fundamentals, Processes and Modelling*. (Walter de Gruyter GmbH & Co. KG, Berlin/Boston. 2012). [Full text]

10. Santos S.C.R., Oliveira A.F.M., Boaventura R.A.R. Bentonitic clay as adsorbent for the decolourisation of dye house effluents. *J. Clean. Prod*. 2016. 126: 667-676. [PubMed]

11. Shcherbakov P.L., Petukhov V.A. Comparative effectiveness of enterosorbents in children with diarrhea. Questions of modern pediatrics. 2005. V. 4. №4: 86-90. [eLIBRARY][Full text]

12. Sarma G.K., Gupta S.S., Bhattacharyya K.G. Adsorption of Crystal violet on raw and acid-treated montmorillonite, K10, in aqueous suspension. *J. Environ. Manag*. 2016. 171: 1-10. [PubMed]

13. Vershinin A.S., Bychkovskikh V.A., Smirnov D.M. Application of enterosorbent Polysorb MP (colloidal silicon dioxide) in the complex therapy of various pathological conditions accompanied by endotoxicosis (literature review). Herald of SUSU. Series "Education, Health Care, Physical Culture". 2013. V. 13. №3: 125-129. [Full text]

14. Nikolaev V.G., Mikhalovskii S.V., Gurina N.M. Modern enterosorbents and mechanisms of their action. *Efferent therapy*. 2005. V. 11. № 4: 3-17. [eLIBRARY][Full text]

15. Yakovleva I.N., Shaposhnikov A.A., Vesenzev A.I., Kovaleva V.U., Zakirova L.R., Shevchenko T.S., Shentseva E.A. A Method for production of phytomineralsorbent, physical and chemical properties of

it, effect on the living systems and the quality of the livestock industry products. *Research result: pharmacology and clinical pharmacology*. 2016. Vol. 2, №2: 119-124. [Full text]

16. Babayan M.L. Application of Smectas in the treatment of diseases of the gastrointestinal tract. *Rus. med. Journal*. 2004. № 16 (12): 972-976. [Full text]

17. Dubouk G.P., Gerom M.C., Tria G.V. Therapeutic use of medical clays in gastroenterology. *Rus. med. Journal*. 2006. V. 8, №1: 35-38. [Full text]

18. Shirobokov V.P., Yankovskii D.S., Dyvent G.S. Prospects for the use of bentonite in the creation of a new type of multiprobiotics. Modern pediatrics. 2008. №4 (21): 143-154. [eLIBRARY]

19. Wang P., Afriyie-Gyawu E., Tang Y., Johnson N.M., Xu L., Tang L., Huebner H.J., Ankrah N.A., Ofori-Adjei D., Ellis W., Jolly P.E., Williams J.H.,Wang J.S., Phillips T.D. NovaSil clay intervention in Ghanaians at high risk for aflatoxicosis: II. Reduction in biomarkers of aflatoxin exposure in blood and urine. *Food Addit Contam.* 2008. 25: 622-634. [PubMed][Full text]

20. Feng S.-S., Mei L., Anitha P., Gan C.W., Zhou W.Y. Poly(lactide)-vitamin E derivative/montmorillonite nanoparticle formulations for the oral delivery of docetaxel. *Biomaterials.* 2009. 30: 3297-3306. [PubMed]

21. Bondarev A.V. “Development of composition and technology of granular dosage form with adsorption action based on montmorillonite clay” (PhD diss., University of Belgorod, 2015). [Full text]

22. Vezentsev A.I., Dudina S.N., Vezentsev A.A. Development of enterosorbent based on clays of the Belgorod region. Scientific reports of BelSU. Ser. Natural. science. 2006. № 3 (23). 4.: 55-59. [Full text]

23. Who (World Health Organization). Bentonite, kaolin, and selected clay minerals.*World health organization, international programme on chemical safety V. 231*. (World Health Organization, Geneva, Switzerland, 2005). [Full text]

24. Artevenko P.D., Posokhova A.V., Tarasenko G.A. Modern medical and biological problems of the use of mineral and organic enterosorbents as components of biologically active food additives. Pacific Medical Journal. 2009. № 1: 29-32. [eLIBRARY][Full text]

25. Zychowski K.E., Elmore S.E., Rychlik K.A., Ly H.J., Pierezan F., Isaiah A., Suchodolski J.S., Hoffmann A.R., Romoser A.A., Phillips T.D. Mitigation of colitis with NovaSil clay therapy. *Dig Dis Sci.* 2015. 60(2): 382-392. [PubMed][Full text]

26. Kevadiya B.D., Bajaj H.C. The Layered silicate, Montmorillonite (MMT) as a drug delivery carrier. *Key Engineering Materials*. 2013. Vol. 571: 111-132. [PubMed]

27. Kevadiya B.D., Thumbar R.P., Rajput M.M., Rajkumar S., Brambhatt H., Joshi G.V., Dangi G.P.,Mody H.M., Gadhia P.K., Bajaj H.C. Montmorillonite/poly-(ε-caprolactone) composites as versatile layered material: reservoirs for anticancer drug and controlled release property. *Eur. J. Pharm. Sci*. 2012. 47: 265-272. [PubMed]

28. Wicklein B., Darder M., Aranda P., Ruiz-Hitzky E. Bio-organoclays based on phospholipids as immobilization hosts for biological species. *Langmuir.* 2010. 26: 5217-5225. [PubMed]

29. Feng S.S., Mei L., Anitha P., Gan C.W., Zhou W. Poly(lactide)-vitamin E derivative/montmorillonite nanoparticle formulations for the oral delivery of docetaxel. *Biomaterials* 2009. 30: 3297-3306. [PubMed]

30. Noyan H., Önal M., Sarıkaya Y. The effect of sulphuric acid activation on the crystallinity, surface area, porosity, surface acidity, and bleaching power of a bentonite. *FoodChem*. 2007. 105: 156-163. [PubMed]

31. Bergaya F., Lagaly G. General introduction: clays, clay minerals, and clay science. In: Bergaya F., Lagaly G. (Eds.). (*Handbook of Clay Science*. Elsevier, Amsterdam, 2013). P. 1-19. [PubMed]

32. Zhu R.L., Chen Q.Z., Zhou Q., Xi Y.F., Zhu J.X., He H.P. Adsorbents based on montmorillonite for contaminant removal from water: a review. *Appl. Clay Sci.* 2016. 123: 239-258. [PubMed]

33. Brigatti M.F., Galan E., Theng B.K.G. Structure and mineralogy of clay minerals. In:Bergaya, F., Lagaly, G. (Eds.). (*Handbook of Clay Science*, Part A, second ed. Elsevier, Amsterdam, 2013): 21-82. [PubMed]

34. Boylu F., Ginku K., Esenli F., Gelik M.S. The separation efficiency of Na-bentonite by hydrocyclone and characterization of hydrocyclone products. *Int. J. Miner. Process*. 2010. 94: 196-202. [PubMed]

35. Sampatakakis S., Linos A., Papadimitriou E., Petralias A., Dalma A., Papasaranti E.S., Christoforidou E., Stoltidis M. Respiratory disease related mortality and morbidity on an island of Greece exposed to perlite and bentonite mining dust. *Int.J. Environ. Res. Public Health.* 2013. 10: 4982-4995. [PubMed][Full text]

36. Nagy N.M., Kónya J. Interfacial Chemistry of Rocks and Soils. *CRC Press Taylor &Francis*. (New York, 2009). [PubMed]

37. Borrelli R.A., Thivent O., Ahn J. Parametric studies on confinement of radionuclide sin the excavated damaged zone due to bentonite type and temperature change. *Phys. Chem. Earth*. 2013. 65: 32-41. [PubMed]

38. Ghadge A.N., Ghangrekar M.M. Development of low cost ceramic separator using mineral cation exchanger to enhance performance of microbial fuel cells. *Electrochim. Acta*. 2015. 166: 320-328. [PubMed]

39. Chen Q.Z., Liu H.M., Zhu R.L., Wang X., Wang S.Y., Zhu J.X., He H.P. Facile synthesis of nitrogen and sulfur co-doped graphene-like carbon materials using methyl blue/montmorillonite composites. *Microporous Mesoporous Mater*. 2016. 225: 137-143. [PubMed][Full text]

40. Nien Y.T., Liao Y.H., Liao P.C. Antibacterial activity of poloxamer-modified montmorillonite clay against E.coli. *Mater.Lett*. 2011. 65: 3092-3094. [PubMed]

41. Oh J.M., Biswick T.T., Choy J.H. Layered nonmaterial’s for green materials. *J. Mater. Chem*. 2009. 19: 2553-2563. [PubMed][Full text]

42. Hanuláková D., Zeman J., Vašíček R., Přikryl R., Kuchovský T. Determination of pore water composition

during long term interaction of bentonite substrates with water media: comparative study. *Appl. ClaySci*. 2013. 80-81: 69-75. [PubMed]

43. Elmoubarki R., Mahjoubi F.Z., Tounsadi H., Moustadraf J., Abdennouri M., Zouhri A., ElAlban A., Barka N. Adsorption of textile dyes on raw and decanted Moroccan clays: kinetics, equilibrium and thermodynamics. *Water Resour. Industry*. 2015. 9: 16-29. [PubMed]

44. Yan L., Qin L., Yu H., Li S., Shan R., Du B. Adsorption of acid dyes from aqueous solution by CTMAB modified bentonite: kinetic and isotherm modelling. *J. Mol. Liq*. 2015. 21: 1074-1081. [PubMed][Full text]

45. Eren E. Adsorption performance and mechanism in binding of azo dye by raw bentonite. *Clean Soil Air Water*. 2010. 38: 758-763. [PubMed]

46. Ngulube T., Gumbo J.R., Masindi V., Maity A. An update on synthetic dyes adsorption onto clay based minerals: A state-of-art review. *Journal of Environmental Management*. 2017. V. 191: 35-57. [Full text]

47. Huang R., Wang B., Yang B., Zheng D., Zhang Z. Equilibrium, kinetic and thermodynamic studies of adsorption of Cd (II) from aqueous solution onto HACC-bentonite. *Desalination*. 2011. 280: 297-304. [PubMed][Full text]

48. Murray H.H. Bentonite applications. In: Murray, H.H. (Ed.). *Developments in Clay Science*. (Elsevier, Amsterdam, 2006), P. 111-130. [PubMed]

49. Fu Y., Chung D.D.L. Coagulation of oil in water using sawdust, bentonite and calcium hydroxide to form floating sheets. *Appl. Clay Sci*. 2011. 53: 634-641. [PubMed][Full text]

50. Barbanti D., D'Orazio M., Versari A. Study on some sorption properties of bentonites for their potential use in food technology. *J. Food Eng*. 1997. 33: 193-206. [eLIBRARY]

51. Allo W.A., Murray H.H. Mineralogy, chemistry and potential applications of a white bentonite in San Juan province, Argentina. *Appl. Clay Sci*. 2004. 25: 237-243. [PubMed]

52. Sidhoum D.A., Socías-Viciana M.M., Ureña-Amate M.D., Derdour A., González-Pradas E., Debbagh-Boutarbouch N. Removal of paraquat from water by an Algerian bentonite. *Appl. Clay Sci*. 2013. 83-84: 441-448. [PubMed][Full text]

53. Yuan G.D., Theng B.K.G., Churchman G.J., Gates W.P. Clays and clay minerals for pollution control. In: Bergaya, F., Lagaly, G. (Eds.). (*Handbook of Clay Science*, Part B, second ed. Elsevier, Amsterdam, 2013): 587-644. [PubMed]

54. Komine H. Simplified evaluation for swelling characteristics of bentonites. *Eng. Geol*. 2004. 71; 256-279. [PubMed][Full text]

55. Liang X., Xu Y., Tan X., Wang L., Sun Y., Lin D., Sun Y., Qin X., Wang Q. Heavy metal adsorbents mercapto and amino functionalized palygorskite: preparation and characterization. *Colloids Surf*. 2013. A426: 98-105. [PubMed]

56. Bui Quang Cu , Nguen Hoai Chao, Vesentsev A.I., Buhanov V.D. , Sokolovsky P.V., Mihaylyukova M.O. The antibacterial properties of modified bentonite deposit tam bo. Research result: pharmacology and clinical pharmacology. Vol. 2, №3 (2016): 63-74. [eLIBRARY][Full text]

57. Elkhalifah A.E.I., Maitra S., Bustam M.A., Murugesan T. Effects of exchanged ammonium cation son structure characteristics and CO_2 adsorption capacities of bentonite clay. *Appl. Clay Sci*. 2013. 83-84: 391-398. [PubMed]

58. Huang Y., Zhang M., Zou H., Li X., Xing M., Fang X., He J. Genetic damage and lipid peroxidation in workers occupationally exposed to organic bentonite particles. *Mutat. Res*. 2013. 751: 40-44. [PubMed]

59. Karagüzel C., Çetinel T., Boylu F., Çinku K., Çelik M.S. Activation of (Na, Ca)-bentonites with soda and MgO and their utilization as drilling mud. *Appl. Clay Sci*. 2010. 48: 398-404. [PubMed]

60. Wallis P.J., Gates W.P., Patti A.F., Scot J.L., Teoh E. Assessing and improving thecatalytic activity of K-10 montmorillonite. *Green Chem*. 2007. 9: 1-8. [Full text]

61. Karimi L., Salem A. The role of bentonite particle size distribution on kinetic of cation exchange capacity. *J. Ind. Eng. Chem*. 2011. 17: 90-95. [PubMed]

62. Komadel P., Madejová J. Acid activation of clay minerals. In: Bergaya F., Lagaly G.(Eds.). (*Handbook of Clay Science*. Elsevier, Amsterdam, 2013). P. 385-409. [PubMed]

63. Murray H.H. Traditional and new applications for kaolin, smectite, and palygorskite: a general overview. *Appl. Clay Sci*. 2000. 17: 207-221. [PubMed]

64. Murray H.H. Bentonite applications. In: Murray, H.H. (Ed.), (*Developments in ClayScience*. Elsevier, Amsterdam, 2006). P. 111-130. [PubMed]

65. Masindi V., Gitari W.M., Ngulube T. Defluoridation of drinking water using Al^{3+}-modified bentonite clay: optimization of fluoride adsorption conditions. *Toxicol. Environ. Chem*. 2014. 96 (9): 1294-1309. [Full text]

66. Sarkar B., Megharaj M., Xi Y., Naidu R. Structural characterisation of Arquad®2HT-75 organobentonites: surface charge characteristics and environmental application. *J. Hazard. Mater*. 2011. 195: 155-161. [PubMed]

67. Ma J., Cui B., Dai J., Li D. Mechanism of adsorption of anionic dye from aqueous solutions onto organobentonite. *J. Hazard. Mater*. 2011. 186: 1758-1765. [PubMed]

68. Masindi V., Gitari W.M., Ngulube T. Kinetics and equilibrium studies for removal of fluoride from underground water using cryptocrystalline magnesite. *J. Water Reuse Desal*. 2015. 1: 282-292. [Full text]

69. López-Galindo A., Viseras C. Pharmaceutical and cosmetic applications of clays. In: Wypych F., Satyanarayana K.G. (Eds.). (*Clay Surfaces: Fundamentals and Applications*. Elsevier, Armsterdam, 2004). P. 267-289. [PubMed]

70. Rodrigues L.A.S., Figueiras A., Veiga F., Freitas R.M., Nunes L.C.C., Silva Filho E.C., Leite C.M.S.,. The systems containing clays and clay minerals from modified drug release:a review. *Colloids Surf. B: Biointerfaces* 2013. 103: 642-651. [PubMed][Full text]

71. Carretero M.I. Clay minerals and their beneficial effects upon human health: a review. *Appl. Clay Sci.* 2002. 2: 155-163. [PubMed][Full text]

72. Viseras C., Cerezo P., Sanchez R., Salcedo I., Aguzzi C. Current challenges in clay minerals for drug delivery. *Appl. Clay Sci*. 2010. 48: 291-295. [PubMed]

73. Zhang W., Ding Y., Boyd S.A., Teppen B.J., Li H. Sorption and desorption of carbamazepine from water by smectite clays. *Chemosphere.* 2010. 81: 954-960. [PubMed]

74. Dong Y., Feng S. Poly(D,L-lactide-co-glycolide)/montmorillonite nanoparticles for oral delivery of anticancer drugs. *Biomaterials* 2005. 26: 6068-6076. [PubMed]

75. Lin F.H., Lee Y.H., Jian C.H., Wonga J.M., Shieha M.J.,Wang C.Y. A study of purified montmorillonite intercalated with 5-fluorouracil as drug carrier. *Biomaterials* 2002. 23: 1983-1987. [PubMed][Full text]

76. Choy J.H., Choi S.J., Oh J.M., Park T. Clay minerals and layered double hydroxidesfor novel biological applications. *Appl. Clay Sci*. 2007. 36: 122-132. [PubMed]

77. Emami-Razavi S.H., Esmaeili N., Forouzannia S.K., Amanpour S., Rabbani S., Alizadeh A.M., Mohagheghi M.A. Effect of bentonite on skin wound healing: experimental study in the rat model. *ActaMed. Iran.* 2006. 44: 235-240. [PubMed][Full text]

78. Dominy N.J., Davoust E., Minekus M. Adaptive function of soil consumption: an in vitro study modeling the human stomach and small intestine. *J. Exp. Biol*. 2004. Vol. 207. Pt. 2: 319-324. [PubMed][Full text]

79. Carretero M.I., Gomes C.S.F., Tateo F. Developments in Clay Science 1. Clays and human health. In: Bergaya F., Theng B.K.G., Lagaly G. (eds) *Handbook of Clay Science*. (Elsevier; Amsterdam, 2006): 717-741. [Full text]

80. Ferrell R.E. Medicinal clay and spiritual healing. *Clays and Clay Minerals*. 2008. 56: 751-760. [PubMed]

81. Wilson M.J. Clay mineralogical and related characteristics of geophagic materials. *Journal of Chemical Ecology*. 2003. 29: 1525-1547. [PubMed][Full text]

82. Carretero M.I., Lagaly G. Clays and health: An introduction. *Applied Clay Science*. 2007. 36: 1-3. [PubMed][Full text]

83. Carretero M.I., Pozo M. Clay and non-clay mineral sin the pharmaceutical industry part I. Excipients and medical applications. *Appl. Clay Sci*. 2009. 46: 73-80. [PubMed]

84. Carretero M.I., Pozo M. Clay and non-clay minerals in the pharmaceutical and cosmetic industries part II. Active ingredients. *Appl. Clay Sci*. 2010. 47: 171-181. [Full text]

85. Vezentsev A.I., Dudina S.N., Vezentsev A.A. Development of enterosorbent based on clays of the Belgorod region. Scientific reports of BelSU. Ser. Natural. science. 2006. № 3 (23). 4.: 55-59. [Full text]

86. Korolkova S.V. "Colloid-chemical properties of montmorillonite-illite clays activated with salt solutions" (PhD diss., University of Belgorod, 2012). [Full text]

87. Liashenko N.V. Peculiarities of enterosorption via nasointestinal probe using sorbent diosmectite. *Klin. Khir*. 2014. Vol. 12: 16-18. [PubMed]

88. Carretero M.I., Gomes C., Tateo F. Clays and human health. In: Bergaya F., Theng B.K.G., Lagaly G. (Eds.). *Handbook of Clay Science*. (Elsevier, Amsterdam, 2006): 717-741. [PubMed]

89. Chernenko V.V, Kharchenko N.V. The influence of smecta on the cytoprotective properties of the mucosa of the digestive canal. *Medical practice*. 2001. № 5–6: 164-166. [eLIBRARY]

90. Zychowski K.E. Mitigation of colitis with NovaSil clay therapy. *Dig. Dis. Sci*. 2015. Vol. 60. № 2: 382-392. [PubMed][Full text]

91. Dupont C., Vernisse B. Anti-diarrheal effects of diosmectite in the treatment of acute diarrhea in children: a review. *Pediatr Drugs*. 2009. 11: 89-99. [PubMed]

92. Polevaya E.V., Vakhitov T.YA. Sitkin S.I. Mechanisms of psyllium action in intestinal infections. *Gastroenterology of Saint-Petersburg*. 2012. 2–3: 10-13. [eLIBRARY][Full text]

93. Zissis G. Evaluation of the therapeutic effect of smectite rotavirus caused gastroenteritis. *Saint Peter's Hospital, Bruxelles (paraitre).* 1985: 275.

94. Weese J.S., Cote N.M., de Gannes R.V. Evaluation of in vitro properties of di-tri-octahedral smectite on clostridial toxins and growth. *Equine Vet J*. 2003. 35: 638-641. [PubMed][Full text]

95. Bukhanov V.D., Vezentsev A.I., Filippova O.V., Nadezhdin S.V., Pankova O.N., Firsova T.I., Mikhailyukova V.O., Tishin A.N. The influence of the concentration of montmorillonite containing sorbent and pH of the culture medium on the antibiotic sensitivity of Escherichia coli, as well as the effect of ground on growth of Escherichia. *Research result: pharmacology and clinical pharmacology*. 2017. Vol. 3. №1: 97-104. [eLIBRARY][Full text]

96. Szajewska H., Guarino A., Hojsak I., Indrio F., Kolacek S., Shamir R., Vandenplas Y., Weizman Z. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr*. 2014. 58(4): 531-539. [PubMed][Full text]

97. Bekhtereva M.K., Ivanova V.V., Kosarova A.M., Semyonova S.G. Effective approaches to the treatment of acute gastroenteritis in children. Medical advice. 2015. №6: 43-46. [eLIBRARY][Full text]

98. Das R.R., Sankar J., Naik S.S. Efficacy and safety of diosmectite in acute childhood diarrhoea: a meta-analysis. *Arch Dis Child*. 2015. 100: 704-712. [PubMed]

99. WHO/UNICEF. *Ending preventable child deaths from pneumonia and diarrhoea by 2025: the integrated*

Global Action Plan for Pneumonia and Diarrhoea (GAPPD). (Geneva: World Health Organization, 2013). [Full text]

100. Khediri F, Mrad AI, Azzouz M, Doughi H, Najjar T, Mathiex-Fortunet H, et al. Efficacy of diosmectite (smecta) in the treatment of acute watery diarrhea in adults: a multicentre, randomized, double-blind, placebo-controlled, parallel group study. *Gastroenterol Res Pract*. 2011. V. 2011: 783196. [PubMed][Full text]

101. Afriyie-Gyawu E., Ankrah N.A., Huebner H.J., Ofosuhene M., Kumi J., Johnson N.M., Tang L., Xu L., Jolly P.E., Ellis W., Ofori-Adjei D., Williams J.H., Wang J.S., Phillips T.D. NovaSil clay intervention in Ghanaians at high risk for aflatoxicosis. I. Study design and clinical outcomes. *Food Addit Contam* 2008. 25: 76-87. [PubMed][Full text]

102. Mitchell N.J., Kumi J., Aleser M., Elmore S.E. et al. Short-Term Safety and Efficacy of Calcium Montmorillonite Clay (UPSN) in Children. *Am. J. Trop. Med. Hyg*. 2014. 91(4): 777-785. [PubMed][Full text]

103. Dupont C., Foo J.L., Garnier P., et al. Oral diosmectite reduces stool output and diarrhea duration in children with acute watery diarrhea. *Clin Gastroenterol Hepatol*. 2009. 7: 456-462. [PubMed][Full text]

104. Mujawr Q.M., Naganoor R., Ali M.D. et al. Efficacy of dioctahedral smectite in acute watery diarrhea in Indian children: a randomized clinical trial. *J Trop Pediatr*. 2012. 58: 63-67. [PubMed]

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