Handbook of Clay Science
Edited by F. Bergaya, B.K.G. Theng and G. Lagaly
Developments in Clay Science, Vol. 1

Chapter 11.6

CLAYS AND CLAY MINERALS AS DRUGS

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Clay therapy is based on the ability of clays and clay minerals to adsorb and retain harmful and toxic substances. The beneficial effects of these materials to human health, notably in the treatment of gastrointestinal disorders, were recognized. Indeed, the eating of clay ('geophagy') was practiced since antiquity in all parts of the world. Among the variety of clays and clay minerals that were used by primitive tribes are bentonite, kaolinite, montmorillonite, smectite, and 'pascalite' (a Ca^{2+}-montmorillonite from Wyoming, USA) (Eaton and Eaton, 1995).

Examination of the diets of certain tribes in the high Andes of South America and central Africa, and those of Australian aborigines, showed that these people use clay to avoid getting stomach-ache, dysentery, and food infections. Indeed, the Quetchus Indians of South America used to dip their potatoes into an aqueous suspension of clay, immediately before eating, in order to prevent the build-up of acidity in the stomach. This dietetic procedure is still being followed by some tribes of American Indians. A similar practice was traditionally carried out on board ships where sailors used clays not only to adsorb odours and moisture but also to treat dysentery, burns, boils, sore mouths, and other internal and external disorders.

Although recent research confirmed that clays and clay minerals possess general curative properties, it is the treatment of disorders that remains the focus of attention. By adsorbing 'aggressors' (infectious factors) of the gastrointestinal mucosa barrier, these materials can serve as both prophylactic and therapeutic agents.

11.6.1. INTERACTIONS OF CLAY MINERALS WITH GASTROINTESTINAL MUCUS

At the surface of the gut, a mucus gel adheres to the epithelial cells of the mucosa. This adherent mucus is dynamic, being continuously secreted by the caliciform cells and regularly eroded by environmental 'aggressors' present in the gut lumen.

The mucus gel is largely composed of glycoprotein polymers, lipids, and proteins, linked together by covalent bonds. As such, it acts as a physical barrier protecting

DOI: 10.1016/S1572-4352(05)01025-1

the mucosa against penetration by extraneous molecules and mechanical injury. By maintaining a pH gradient and competing with the epithelial surface for micro-organisms, the mucus gel also acts as a chemical barrier.

Thus, a weakening of the mucus gel barrier may be at the origin of disorders such as gastritis and colitis (Droy-Lefaix, 1987). Short-term treatment with clay minerals, such as smectites (Moré et al., 1987) and attapulgite (Moré et al., 1992) increases the thickness of the adherent mucus. This may be ascribed to interactions of mineral particles with mucus components (Leonard et al., 1994) by which the gastrointestinal glycoproteins are modified, and their polymerization is enhanced (Droy-Lefaix et al., 1986). Similarly, aluminium (hydr)oxides (e.g., boehmite) can reduce mucus degradation (Bouyssou et al., 1990). The beneficial effects of minerals are also associated with improvements in the rheological properties of the mucus gel, such as spinability. This reflects the increased extent of polymerization, and the improvement in quality, of the adherent mucus (Droy-Lefaix et al., 1985). Changes in the physico-chemical properties of the mucus, induced by the action of clay minerals, were confirmed by electron paramagnetic resonance and fluorescence spectroscopy. The results indicate that clay mineral ingestion decreases mucus solubility. At the same time, the viscosity and hydrophobicity of the mucus increases, enhancing its adhesion to epithelial cells.

11.6.2. CLAY MINERALS, MUCOSAL BARRIER, AND GASTROINTESTINAL 'AGGRESSORS'

By acting directly on the mucus gel, clays and clay minerals exert a stabilizing effect on the mucosal barrier (Gwozdzinski et al., 1997), providing protection against different 'aggressors' of the gastrointestinal mucosa.

Pepsin, a substance necessary for digestion, is a typical 'aggressor'. Experiments with rats showed that if pepsin secretion at the surface of the gastric mucosa is strongly increased (due to pathological disregulation), the adherent mucus layer is progressively disrupted. At the same time haemorrhagic mucosal lesions appear, and significant bleeding occurs in the lumen as well as localized ulceration in an otherwise intact epithelium. By binding to the mucus components, smectite can completely inhibit the damage induced by pepsin (Leonard et al., 1994).

Samson et al. (1995), for example, showed that patients with ulcerative colitis show a six-fold greater mean total faecal proteinase activity (expressed in mmol terminal NH_2/min/g dry weight of faeces) than the control. Smectite totally inhibits this enzyme activity. The effects of smectite on mucus proteolysis are assessed using a model of mucolytic activity, assayed by the release of degraded colonic mucin from the adherent mucus gel of freshly prepared pig colonic bags in vitro. Similarly, trypsin (2 mg/mL) releases three times more soluble mucin per bag than the control. Smectite (100 mg/mL) inhibits trypsin activity, causing the level of degraded mucin to fall below the normal value. This is ascribed to the interaction of smectite

with the adherent mucus layer, and the binding of trypsin to the mineral (Samson et al., 1995).

Clay minerals can also provide protection against attack by bile acids that cause gastrointestinal ulceration. In rats, oral administration of sodium glycodeoxycholate or sodium taurocholate induces severe erosion of the jejunal mucosa. After treatment with smectite (which interacts closely with the mucus glycoproteins) the severity of surface erosion is greatly diminished (Fioramonti et al., 1990), while the rheological properties of the adherent mucus gel are maintained within normal limits (Droy-Lefaix et al., 1985).

Because of their strong bioadhesive properties, clay minerals also afford protection of the colon against damage from reactive oxygen species. Oxygenated free radicals, released by infiltration of white cells into the colonic mucosa barrier, are very unstable. Their presence can induce severe erosion of the colonic mucosa, leading to mucolysis. By maintaining the solution viscosity of the colonic mucin, and inhibiting the hypersecretion of mucus, smectite can prevent the onset of mucolysis (Pearson et al., 1996; Knight et al., 1998).

In many digestive diseases, the intestinal barrier is weakened by the release of pro-inflammatory cytokines, induced by abnormal activation of the epithelial cells and the underlying immune system. These cytokines include a tumour necrosis factor–α (TNF-α) and an interferon-γ factor (INF-γ). When intestinal cells (line HT 29-19 A) are incubated with TNF-α and INF-γ, intestinal function (assessed in Ussing chambers by measuring ionic conductance, apicobasal fluxes of ^{14}C-mannitol, and intact horseradish peroxidase) is altered, and the tight junction between cells is disrupted. In the presence of smectite (100 mg/mL) the values of these parameters are similar to those of the control (Mahraoui et al., 1997).

The cytoprotective effects of clay minerals can also account for their ability to prevent damage of the gastrointestinal mucosa caused by such 'aggressors' as ethanol and anti-inflammatory drugs. Ethanol, directly administered into the stomach, gives rise to severe gastric ulcerations and macroscopic necrosis of the gastric mucosa. These deleterious effects are accompanied by a decrease in the gastric transmural potential difference which serves as a criterion of the functional integrity of the mucosa (Fioramonti et al., 1990). Erosion of the mucus layer leads to a significant alteration of rheological properties (Droy-Lefaix et al., 1992; Slitine-Bonet et al., 1994). Smectite treatment for two days can significantly counteract the harmful effect of ethanol, reducing the irritative index (Fioramonti et al., 1990).

Clay minerals also provide protection against the action of anti-inflammatory drugs. For example, the oral administration of aspirin (2 g) to pigs, and phenylbutazone (200 mg/kg) to rats, decreases the gastric potential difference, and induces severe ulceration due to mucus alteration (Fioramonti et al., 1990; Droy-Lefaix et al., 1992). The extent of lesion and mucus degradation is significantly reduced after treatment with smectite. In humans the symptoms of gastropathies, induced by non-steroid anti-inflammatory drugs, can be successfully treated by ingestion of smectite (Peignot et al., 1997).

11.6.3. ADSORPTIVE PROPERTIES OF CLAYS AND CLAY MINERALS

The adsorptive properties of clay minerals provide the basis for the therapeutic uses of clays.

A. Toxins

Clays can adsorb a variety of toxic substances, such as strychnine (Droy-Lefaix, 1986), mycotoxins (e.g., T2 toxin) (Fioramonti et al., 1987b), aflatoxin (Schell et al., 1993), enterotoxins (Brouillard and Rateau, 1989), and toxins produced by *Vibrio cholerae*, *Escherichia coli* (Fioramonti et al., 1987b), and *Yersinia pseudotuberculosis* (Carnoy et al., 2000).

By doing so, clays can provide active protection against disturbances during gastrointestinal transit. In mice, for example, gastric emptying and small intestinal transit are significantly accelerated after oral administration (1 mg/kg for 4 days) of T2 toxin. However, if the toxin is incubated with smectite for 24 h beforehand, no increase in the rate of gastric emptying and small intestinal transit occurs (Fioramonti et al., 1987a).

In conscious dogs, intraduodenal administration of cholera toxin (200 mg) affects gastrointestinal transit, and disrupts the migrating motor complexes (MMCs) of the stomach and jejunum. According to the duration of treatment (at a dose of 100 mg/kg/day), smectite can effectively counteract the effects of cholera toxin (Fioramonti et al., 1987b).

Smectite can also adsorb the enterotoxin of *Clostridium difficile* (Martirosian et al., 1998). In rats, this toxin causes intestinal permeability to increase through hypersecretion of colonic water. Both these conditions can be alleviated by treatment with ^{51}Cr-EDTA in the presence of smectite (Fioramonti et al., 1994).

E. coli toxin is an infectious agent causing diarrhoea. Heat-stable toxin (ST) from *E. coli*, directly administered to New Zealand rabbits, induces a significant increase in intestinal permeability (as estimated by Evans Blue) and severe damage to ileal loops (as revealed by scanning electron microscopy). The presence of smectite in the ileal loops has a protective effect (Pons et al., 1997).

Similar results are obtained with the enterotoxin of *Bacteroides fragilis* administered to HT/29 C1 cells (human colon adenocarcinoma cell line). Prior incubation of this toxin with smectite suppresses its toxic effects (Martirosian et al., 1998).

B. Pesticides

Because of their high adsorptive capacity, clay minerals can also protect the digestive mucosa against pesticide damage. Diquat, a widely used non-selective desiccant herbicide, induces erosion of intestinal mucosa and fluid hypersecretion. In rats that were given diquat, treatment with smectite (500 mg/kg for 2 weeks) brings about a normalization of mucus rheological properties and intestinal permeability, as

indicated by urine analysis using ^{51}Cr-EDTA (Theodorou et al., 1995). Similarly, montmorillonite and bentonite are good adsorbents, and may be recommended for the treatment of pesticide poisoning (Meredith and Vale, 1987).

C. Microorganisms

Clay minerals are efficient drugs for treating disorders of the gastrointestinal mucosa, induced by microorganisms. Kaolinite and montmorillonite are capable of adsorbing viruses (Lipson and Stotzky, 1984). As such, these minerals can induce rapid recovery when administered to children suffering from gastroenteritis. Similarly, the strong adsorptive power of smectite lies behind its ability to aggregate bacteria, such as strains of *E. coli* with the plasmid P, carrying a virulence factor in the form of an external protein CS 31A (Girardeau, 1987).

In the stomach, *Helicobacter pylori* is associated with gastritis and gastroduodenal ulcers. This bacterium is also one of the most important ethiopathogenic factors causing peptic ulcer. Smectite, on HeLa cells infected by *H. pylori* isolated from human biopsies, significantly reduces adhesion of the bacteria to the surface of epithelial cells (Bonneville et al., 1990). This is why smectite is effective in treating the symptoms of people with non-ulcer dyspepsia who are infected by *H. pylori* (De Korwin et al., 1993).

In the intestine, smectite is effective against diarrhoea as shown by clinical data for new-born calves with neonatal gastroenteritis. Faeces analysis reveals the presence of rotavirus in 41.3% of the animals as well as that of *E. coli* K99, coronavirus, and Salmonella. Recovery is observed in 72% of calves after 2.8 and 2.2 days of receiving 250 and 500 mg/kg smectite, respectively, and after 4.2 days in calves which do not receive smectite. After 4 days of treatment, the consistency of the faeces is significantly better in calves receiving smectite than in the control animals (Espinasse et al., 1987).

D. Gas

Clay minerals can serve as gas adsorbents in patients with symptoms of flatulence and abdominal distension. Thus, smectite can reduce the amount of hydrogen emitted during colonic fermentation (Frexinos et al., 1986; Arbeille et al., 1991).

E. Alimentary Allergy

Food allergy is also responsible for disturbances in colonic transit, water absorption, and intestinal permeability. Guinea pigs that were sensitized by β-lactoglobulin from cow milk show colonic transit acceleration, a colonic hypersecretory response, a strong increase in intestinal permeability, and a decrease in faecal dry matter. These effects are not observed in animals that were treated with smectite. Clays can inhibit anaphylaxia probably by controlling the release of mediators at the origin of the degranulation of the mast cells (Theodorou et al., 1994).

11.6.4. CLAY MINERALS AND CLINICAL APPLICATIONS

Being good adsorbents and mucostabilizers, clay minerals are efficacious against several aggressive agents causing severe intestinal disorders. Acute gastroenteritis is a major cause of morbidity and mortality among children worldwide (Madkour et al., 1993). By adsorbing viruses, bacteria, and other digestive irritants, clay minerals can shorten the course of acute diarrhoea, and reduce the occurrence of prolonged diarrhoea. Furthermore, these minerals do not interfere with the electrolyte balance, and are well tolerated by patients (Buttron, 1987; DuPont et al., 1990; Bauer and Hirschbrunn, 1992; Charritat et al., 1992; Dupont et al., 1992; Vivatvakin et al., 1992; Lexomboon et al., 1994; Karas, 1996; Milocco et al., 1999; Guarino et al., 2001; Narkeviciute et al., 2002).

Clay minerals also provide protection against diarrhoeas induced by antibiotics treatments (Benhamou et al., 1995), alleviate chronic diarrhoeas induced by chemotherapy and radiation (Hornbrink et al., 1995; Ippolite, 1998; Santantonio et al., 2000), enteral nutrition (Perrotin et al., 1990), and HIV infection (Phanuphak et al., 1992; Mastroianni et al., 1998).

Clay minerals are promising drugs in the treatment of irritable bowel syndrome (IBS), a rather frequent disease in adults with a complex pathogenic mechanism. By enhancing the thickness of the mucus barrier, both colon movement function and faeces consistency are restored, and the symptoms of IBS are alleviated (Opriu et al., 1996; Secondulfo et al., 2002). In parallel, clay minerals have a positive effect on flatulence and abdominal distension (Lukas and Lukas, 2000).

11.6.5. CONCLUSIONS

Clay minerals protect and are efficient against several 'aggressors' that cause major disorders of the gut. These beneficial effects of clay minerals (on the gastrointestinal mucosa) are associated with two mechanisms of action: (1) adsorption of the 'aggressors' or their toxic secretions and (2) modification of the thickness and rheological properties of the adherent mucus, reinforcing the natural defenses of the gastrointestinal mucosa.

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