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Revisión

Zeolite: "the magic stone"; main nutritional, environmental, experimental and clinical fields of application

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Abstract

Introduction: **zeolites (clinoptilolites) are a family of alluminosilicates and cations clustered to form macro aggregates by small individual cavities. In the medical area they are involved in detoxification mechanisms capturing ions and molecules into their holes. Actually, we classify about 140 types of natural and 150 synthetic zeolites, for specific and selective use. Clinoptilolite is a natural zeolite and it is the most widespread compound in the medical market.**

Objective: **this review analyzes the main fields of zeolite utilization.**

Methods: **we searched Pubmed/Medline using the terms "zeolite" and "clinoptilolite".**

Results and discussion: **in zoothechnology and veterinary medicine zeolite improves the pets' fitness, removes radioactive elements, aflatoxines and poisons. Zeolite displays also antioxidant, whitening, hemostatic and anti-diarrhoic properties, projected in human care. However very scanty clinical studies have been run up to now in immunodeficiency, oncology after chemotherapy and radiotherapy as adjuvants.**

Conclusions: **further clinical investigations are urgently required after this review article publication which updates the state of the art.**

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Key words: *Alluminosilicates. Clinoptilolite. Detoxification. Nutrition.*

ZEOLITA: "LA PIEDRA MÁGICA"; PRINCIPALES CAMPOS NUTRICIONALES, AMBIENTALES, EXPERIMENTALES Y CLÍNICOS DE LA APLICACIÓN

Resumen

Introducción: **las zeolitas (clinoptilolitas) son una familia de aluminosilicatos y cationes agrupada para formar agregados macro de pequeñas cavidades individuales. En el área médica están involucrados en los mecanismos de desintoxicación y en capturar iones y moléculas en sus agujeros. En realidad, clasificamos cerca de 140 tipos de zeolitas naturales y 150 sintéticas, para usos específicos y selectivos. La clinoptilolita es una zeolita natural y es el compuesto más extendido en el mercado médico.**

Objetivo: **esta revisión analiza los principales campos de utilización de la zeolita.**

Métodos: **se realizaron búsquedas en Pubmed/Medline usando los términos "zeolita" y "clinoptilolita".**

Resultados y discusión: **en zootecnología y medicina veterinaria la zeolita mejora la condición de la mascota, elimina los elementos radiactivos, las aflatoxinas y los venenos. En el cuidado humano, la zeolita también muestra propiedades antioxidantes, de blanqueamiento, homeostáticas y antidiarreicas. Sin embargo, los estudios clínicos que se han llevado a cabo hasta ahora como adyuvante en inmunodeficiencia y tras la quimioterapia y la radioterapia en oncología son muy escasos.**

Conclusiones: **se requieren con urgencia otras investigaciones clínicas después de esta publicación del artículo que actualicen el estado de la técnica.**

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Palabras clave: *Aluminosilicatos. Clinoptilolita. Desintoxicación. Nutrición.*

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Abbreviations

DMMP: dimethyl phosphonate.
TBTCl: tributilin chlorine.
FeZW: iron-zeolite.
$CdCl_2$: cadmium chloride.
ZEOFe: iron zeolite.
HSCAS: sodium, calcium hydrate aluminosilicate.
ROS: reactive species of oxygen.
QC: QuickClot standard.
ACS: QuickClot bagged.
ENGORD: endoscopically negative gastroesophageal reflux disease.

Introduction

Chemical-physical characteristics

The zeolites (clinoptilolites) are a mineral family having a regular micro porous crystalline structure with multiple micro cavities inside the crystals[1].

The structure is based on aluminosilicates ($Na_{12}[(-SiO_2)_{12}(AlO_2)_{12}]\cdot 27H_2O$) and cations trapped into micro cavities.

In the modern medical practice there are many siliceous or calcareous inert compounds. They are summarized in Table I.

Zeolites are "molecular sieves" with greater chemical selectivity compared to silica and active carbon[1]. In fact silica and aluminum atoms are in the center of a tetrahedron where at the vertex there are oxygen atoms. The scaffolding is made of multiple cavities which may be filled up by water molecules and heavy metals. Water molecules may be loosed if the mineral is exposed at the open air or if it is heated. So zeolites can exchange ionic metals in the cavities with other metals: for example if a sodium zeolite is embedded by concentrated potassium solution , it will be modified in potassium zeolite[1].

The pores sizes modulates the catalytic property of zeolites: the molecules selectively entered into the pores are subsequently exposed to cracking and isomerization reactions. Moreover the cations quality trapped in the zeolite affects the kinetic of the ion exchange.

Table I
Aluminosilicates compounds employed in the medical practice.

	Chemical-physical characteristics	*Therapeutic applications*
Clinoptilolite (Zeolite)	Natural zeolite; the crystalline structure is composed of two tetrahedrons of SiO_4 and AlO_4 linked with oxygen bonds. The scaffolding has multiple free spaces and canals where cations and molecules may be located	Sustain the immune system Balance the body pH Reduce the free radicals Neutralize and/or eliminate noxious substances (toxins, heavy metals, ammonium, nitrosamines) Improve the tissues oxygenation Stimulate the skin regeneration of wounds, wheals, skin reddening, acne and psoriasis Improve the general health condition Coadjutant in different pathologies, such as in cancer Reduce collateral effects of chemotherapy and radiotherapy Anti-hemorrhage
Clay	Granules dimensions < 2 μm of diameter; it is mostly formed of hydrate aluminosilicates (phyllosilicates); adsorbent properties water molecules; ionic exchange properties and fission of cations	Gastrointestinal disorders
Caoline	Sedimentary stone formed mostly of caolinite, a siliceous mineral of clays	Production of synthetic zeolites Therapeutic treatment of acute diarrhea Pharmacological excipient (anti-mycosis and anti-emetic drugs)
Bentonite	Phyllosilicate, aluminosilicates; clay mineral formed mostly of montmorillonite, calcium and sodium	In diet it is employed in association to psillium in order to remove ancient residues of mucus and excrements from the gut
Diosmectite	Aluminum and magnesium silicate, insoluble in water	Gut adsorbent in the treatment of gastrointestinal disorders (symptomatic treatment of esophagus, stomach and gut painful diseases, GERD, hiatal hernia, colitis, meteorism, bulbitis, gastro duodenal ulcer, chronic and acute diarrhea)
Attapulgite	Magnesium hydrate aluminosilicate mineral, formed of clays;	Antacid and anti-diarrhea thanks to toxins and gut bacteria adsorbent properties

Actually about 40 kinds of natural zeolites are classified , and about 150 have been synthetized for specific applications[2]. Of the 40 natural zeolites, clinoptilolite, mordenite and chabazite have a very important commercial role. Clinoptilolite possesses a crystalline structure based on two thetraedrons of SiO_4 ed AlO_4 linked by oxygen bonds. Canals and free spaces of its framework hold cations and relatively big molecules. Clinoptilolite is the activated zeolite in uptaking and output promoting of water and soil pollutants, being therefore most widely used in human and animals[1].

Synthetic zeolites can artificially be produced submitting minerals to high pressures in autoclaves. For example, it can be synthetized at 10000-20000 °C, heating a hydroxide tetrapropylammonium solution (which functions as a template) with colloidal silica and micro porous aluminum. Permutites are synthetic zeolites produced solubilizing mixtures of quartz, caolinum and sodium carbonate; many of these possess better mechanic and ionic exchange properties compared to natural zeolites.

Rewiew

Applications

Zeolites are basically cations exchanger by a chemical-physical process where the cation in the crystalline structure is exchanged with the solution ions of similar size and electro-static properties. For example, natural zeolites exchange Na^+ o K^+ ions with Ca^{2+} e Mg^{2+} ions[3]. Recently, the conductivity of zeolite was investigated to evaluate the property of volatile compounds detection , (such as butane, ammoniac, and dimethyl phosphonate (DMMP)) due to its binding property to gas molecules in the pores[4].

This review investigates the most important environmental, experimental and clinical fields of natural and synthetic zeolites application.

Environemental evidences

Harris JA and Birch P[5] investigated in fungi (*Aspergillus niger*, *Botrytis cinerea* e *Fusarium culmorum*) cultures the effect of clinoptilolite 3% on the lead toxicity (100-500-1000 mg dm^{-3}). A reduction of 25% of the growth inhibition of *A.niger* and *B. cinerea* was observed at 1000 mg dm^{-3} of lead, and of *F.culmorum* at all the experimental concentrations of lead. The mechanism of action of clinoptilolite is based on the absorption of lead, which concentration consequently decreases and also the fungal toxicity.

Ohta M et al.[6] exposed *Euglena gracilis* cells to tributilin chlorine (TBTCl) 100 μM 5% to iron – zeolite (FeZW) contamination for 3 hours. The FeZW reduced TBTCl concentrations from 22.50 μg/ g to 7.53 μg/g cell. This compound can be effectively used in detoxification of contaminated water by heavy metals.

Liu CH and Lo KV[7] showed an ammonium clearance, range by zeolite between 20% to 98%. Furthermore the synthetic zeolite 4A (40-50 μg/l) added to a depurative water filter significantly reduced iodide, iodate, cesium and barium concentrations respectively of 85%, 40%, 75-90% and >85% ($P<0.05$).

Zorpas AA et al.[8] evaluated the efficacy of 25% zeolite in removal of heavy metals from the compost. 2.4 + 0.3 meq/g represented the amount of exchangeable cations (Na, K, Ca and Mg). Zeolite up took 12% of Co, 27% of Cu, 14% of Cr, 30% of Fe, 40% of Zn, 55% of Pb and 60% of Ni.

Haidouti C[9] investigated the efficacy of zeolite 1%, 2% and 5% in clearing mercury from contaminated soils. The concentrations were reduced up to 86% in shoots and up tp 58.2% in roots of soils contaminated plants , compare to untreated.

Table II summarizes studies analyzed in this paragraph.

In vivo experimental evidences

Olver MD[10] observed that a diet supplementation with 50 g/kg of clinoptilolite for 28 days in 120 chickens at 16 years old, improves significantly the number of lay eggs, the thickness of the shell, the utilization of the food and the humidity of excrements ($P<0.01$).

Pond WG and Yen JT[11] investigated the anti-anemia properties of clinoptilolite 3% and synthetic zeolite (NaZ) administered for 31 days. Weanling Landrace X Yorkshire pigs were enrolled. They received a dose of cadmium chloride ($CdCl_2$ - 150 ppm) at first whose concentration was reduced after zeolites from 16.6 ppm to 11.4 ppm administration. Any variations of the hepatic iron and of the renal cadmium were observed in both the treatments. Instead zinc concentrations increased after the administration of NaZ ($P<0.001$). In conclusion zeolites may offer a partial protection from iron-deficiency anemia induced by $CdCl_2$.

Jandl J and Novosad J[12] investigated the effects of 50 g/die of iron-zeolite (ZEOFe). ZEOFe effectively reduces the concentration of radioactive cesium-137 from 15 to 50 times, suppressing the enteral cycle of the cesium.

Katsoulos PD et al.[13] analyzed the effects of diet supplementation in 52 Holstein cows with clinoptilolite 1.25% and 2.5% toward the concentration of copper, zinc and iron. At the end of the experimental study the supplementation did not impair the metal concentrations.

Parlat SS et al.[14] published the effects of 50 k/kg of clinoptilolite in the toxicity of 2 mg total aflatoxins (AF 83,06 %: AFB1 , 12.98 % AFB2 , 2,84 % AFG1 and 1.12 % AFG2/kg). Aflatoxins were introduced in the diet of 40 chicks aged from 10 to 45 days, for 4 weeks. The authors detected an higher food intake in

Table II
Environmental studies of zeolites

Application	*Zeolite concentration*	*Sample*	*Results*	*References*
Clinoptilolite effects on lead toxicity (100-500-1000 mg dm^{-3} in fungi	Clinoptilolite 3%	*Aspergillus niger, Botrytis cinerea* and *Fusarium culmorum*	Reduction of 25% of the growth inhibition of *A.niger* and *B.cinerea* at 1000 mg dm^{-3} of lead; almost a total reduction of the growth inhibition of *F.culmorum* at all the concentrations investigated	5
Effects of FeZW in water detoxification	FeZW 5% zeolite for 3 hours	*Euglena gracilis*	Intracellular concentrations reduction of TBTCl (22.50 μg/g cell absence of FeZW vs 7.53 μg/g cell presence of FeZW	6
Effects of zeolite in water depuration (domestic filter	Synthetic zeolite 4A	Water iodide, iodate, cesium, barium (concentrations 40-50 μg/l	Significant reduction of iodide (85%, iodate (40%, cesium (75-90% and barium (>85%; $P<0.05$	24
Effects of zeolite in the removal of NH_4^+ from the compost	-	Compost	NH_4^+ removal of 98% in the total volume	7
Effects of zeolite in the removal of heavy metals from the compost	25% zeolite	Compost	Zeolite took up to 12% of Co, 27% of Cu, 14% of Cr, 30% of Fe, 40% of Zn, 55% of Pb and 60% of Ni	8
Effects of zeolite in the removal of mercury from contaminated soils	zeolite 1%, 2% and 5%	Plants living in contaminated soils	Mercury concentrations were reduced up to 86% in shoots and up tp 58.2% in roots of plants living in contaminated soils, respect to controls, not treated.	9

the group treated with clinoptilolite (6%), respect to the untreated controls, (14%). The body weight gain was inferior in chicks treated with clinoptilolite (8%) respect to the control group (27%). The addiction of aflatoxins to diet in fact is responsible of the reduction of food consumption and consequently to the loss of body weight[15] due to imbalance of pancreatic and liver enzymes[15,16].

Mayura K et al.[17] evaluated the putative role of sodium calcium hydrate aluminosilicate (HSCAS 5 g/kg), an adsorbent compound derived from zeolite and montmorillonite, against experimental aflatoxicosis in rats (2.5 mg/kg of AFs). The administration of both the compounds produced a significant improvement of hematologic and biochemical parameters (hemoglobin, erythrocytes, leucocytes, cholesterol, triglycerides, cholinesterase, total proteins, albumin, zinc, copper, creatinine, bilirubin, ureic nitrogen, alkaline phosphatase and transaminase; $P<0.05$), which values were altered after the poisoning.

Cefali EA et al.[18] compared the increase of the bioavaiability of silicon from different compounds (zeolite A 30 mg/kg, sodium aluminosilicate (16 mg/kg), magnesium aluminosilicate (20 mg/kg) and aluminum hydroxide (675 mg/kg), administered only one time in 12 female beagles. Plasma samples were rescued and analyzed after 24 hours. Results showed that only zeolite A significantly increased the plasmatic silicon levels (9.5 ± 4.5 mg hr/L $\pm$ SD; $P=0.041$). Consequently zeolite A may be effective in the treatment of osteoporosis thanks to the stimulation of bones growth, induced by the increase of silicon bioaivalability.

Zeolite properties were also investigated at a cerebral level. Montinaro M et al[19] studied in a model of Alzheimer diseases mice the antioxidant and neuroprotective properties of clinoptilolite, which was administered through the water beverage (0.6 – 1.25 – 2.5 ng/ml) for 5 months. A significant reduction of the cellular death induced by reactive species of oxygen (ROS) was induced ($P<0.001$) in the group treated with clinoptilolite respect to the control group, not treated; it was also observed a significant increase of ROS production in mitochondria ($P<0.001$), a significant increase of the activity of superoxide dismutase enzyme in the hippocampus of mice ($P<0.01$), and a significant reduction of the levels of the amyloids plaques ($P<0.05$). The authors suggest clinoptilolite as a potential coadjutant in the therapeutic treatment of Alzheimer disease.

Nistiar F et al.[20] investigated in rats pre- poisoned with the pesticide dichlorvos (200 – 128 – 81.9 – 65.5 and 52.4 mg/kg) the properties of oral clinoptilolite (1 g/kg). Cholinesterase activity was investigated in different tissues. A significant reduction of the cholinesterase inhibition was observed after the administration of clinoptilolite ($P<0.01$).

Mojzis J et al.[21] investigated the effects of tuff zeolite (composed of 61% of clinoptilolite) in the modulation of cholinesterase activity in different tissues of rats. Rats were poisoned with VX substance (65.5 μg/g), a synthetic nerurotoxic compound. Tuff zeolite was administered 5 minutes before the poisoning. Results showed a significant reduction of the inhibition of cholinesterase activity in all the tissues investigated ($P<0.001$).

Tátrai E and Ungváry G[22] studied in 100 rats the potential toxic effects of clinoptilolite (0, 30, and 60 mg), intratracheally administered to evaluate multivisceral cancer risk. Any increase of the tumor incidence in organs and in tissues was verified.

In the coagulation area, Arnauld F et al.[23] evaluated the hemostatic properties of a zeolite medical device (QuikClot bagged – ACS (The ACS was a new formulation of the traditional QuikClot – granular (QC).). Hemorrhages were induced on 32 Yorkshire pigs by full transection of the femoral vasculature. Blood loss was significantly inferior in the groups treated with QuikClot devices (7.4% QC and 10.3% ACS), compared with standard medications (22.3%). The time to death was major in the groups treated with QuikClot devices (188 minutes QC and 194 minutes ACS) respect to the group treated with standard medications (96.8 minutes). The 4 hours global survival was significantly major in the groups treated with QC and ACS devices (6/8; 75%) compared with the standard medications (1/8; 12.5%). Confirming the role of ACS medical device in the control of hemorrhages.

Shin YJ et al.[24] observed that a synthetic zeolite (zeolite 4A) inhibited melanin in vitro production in a dose-effect ratio ($P<0.001$). In melanoma cells B16F10 incubated for 24 hours with zeolite 4A at concentrations between 0.16 and 100 μg/ml. The cancerogenesis may be based on a direct blockage of the α-MSH hormone by tyrosinase enzyme. Consequently a reduction of the expression of the melanocytic tyrosinase and a suppression of melanogenesis-ERK modulated, were verified. These results suggest a potential use of zeolite as a whitening agent of the skin.

Norouzian MA et al.[25] realized a supplementation with 1.5% and 3% of clinoptilolite for 6 weeks to the diet of 30 newborns lambs. The anti-diarrhea properties, the hematocrit levels, the plasmatic fibrinogen and total proteins were evaluated. At the end of the experimental study both the concentrations tested reduced significantly the diarrhea gravity index, without influencing others parameters investigated ($P<0.05$). Mallek Z et al.[26] observed that a diet supplementation with clinoptilolite 0.5% and 1% for 45 days in 200 chickens, reduced significantly the microbial infection of the gut ($P<0.05$), increased the growth rate ($P<0.05$), increased the body weight ($P<0.05$) and increased the levels of n-3 polyunsatured fatty acids ($P<0.05$).

Katic M et al.[27] investigated the effects of clinoptilolite 85% on cells viability thanks to the modulation of key proteins and key genes. Mouse fibrosarcoma cells, small cells carcinoma, human pancreas carcinoma cells were cultured with clinoptilolite. After 24 hours of incubation the number of viable cells, the DNA synthesis, the activity of EGF-R, pKB/Akt and NFKB were significantly reduced ($P<0.01$). Probably the absorption of clinoptilolite by tumor cells in the medium interfere with calcium levels and with calcium signaling pathway. In this way clinoptilolite may be considered as a potential adjuvant in cancer therapy.

Mohri M et al.[28] evaluated the effects of a clinoptilolite supplementation in 30 calves, in order to improve health status and to prevent mycotoxins intoxication[28]. Clinoptilolite was added to the colostrum milk in concentrations of 2% for 2 days (Group 1) and 2% for 14 days (Group 2). Blood samples were analyzed 12 hours after the birth of calves and at the end of the first, the second, the third, the fourth, the fifth and the sixth weeks of life. Serum plasma fibrinogen, total albumin, beta and gamma globulin were significantly higher in Group 2 ($P<0.05$) suggesting a beneficial effect of clinoptilolite supplementation to the health status of calves.

Katsoulos PD et al.[29] studied the effects of clinoptilolite on clinical ketosis of 52 Holstein cows. Particularly, 17 cows were fed with 1.25% of clinoptilolite for 4 weeks (Group 1); 17 cows were fed with 2.5% of clinoptilolite for 4 weeks (Group 2); and 18 cows did not receive any supplementation (Group 3, control). At the end of the experimental period, cows of Group 1 and Group 2 showed a significant reduction of ketosis ($P<0.01$) respect to Group 3.

Ortatatli M et al.[30] investigated the protective effects of clinoptilolite (15 g/Kg) against aflatoxicose induced by 100 ppb of aflatoxins in 576 broilers. A significant hydropic degeneration, a bile duct hyperplasia and a periportal fibrosis were found in chickens fed with aflatoxins ($P<0.05$). After 42 days of supplementation with clinoptilolite the number of affected chickens and the organs degeneration were significantly inferior ($P<0.05$).

Table III summarizes studies analyzed in this paragraph.

Clinical evidences

Ivkovic S et al.[31] investigated the supplementation with two clinoptilolite dietary supplements (Megamin 3.6 g/die and Lycopenomin 1.2 g/die) in 61 immunocompromised patients. Supplementation lasted from 6 to 8 weeks. At the end of the observational period the blood count was not modified from the supplements, while a significant increase of lymphocytes $CD4^+$ and $CD19^+$, and a significant reduction of lymphocytes $CD56^+$ were observed in patients treated with Megamin. Instead, Lycopenomin was associated to a significant increase of lymphocytes $CD3^+$ and also to

Table III
Experimental studies of zeolite

Application	*Zeolite concentrations*	*Sample*	*Results*	*References*
Effects of diet supplementation with clinoptilolite	50 g/kg of clinoptilolite for 28 days	120 chickens	Significant effects of supplementation on the number of lay eggs, on thickness of the shells, on the utilization of the food and on the humidity of excrements (P<0.01)	10
Anti-anemia effects of clinoptilolite and of synthetic zeolite	Clinoptilolite and synthetic zeolite (NaZ) 3% for 31 days	Weanling Landrace X Yorkshire pigs	Reduction of Cd levels (after treatment 11.4 ppm vs before treatment 16.6 ppm); No hepatic Fe levels modifications; increase of Zn concentrations (P<0.001)	11
Effects on the bioavailability of radioactive Cs-137	50 g/day of iron-zeolite (ZEOFe)	Ovine	Reduction of the equilibrium concentrations of Cs-137 from 15 to 50 times	12
Effects of diet supplementation with clinoptilolite	Clinoptilolite 1.25% and 2.5%	52 Holstein cows	The concentrations investigated did not negatively interfere on serum concentrations of Cu, Zn and Fe in cows	13
Effects of clinoptilolite in the reduction of aflatoxins concentrations	Clinoptilolite 50 g/kg for 4 weeks	40 newborns chicks	Inferior reduction of food consumption (6%) in the group treated with clinoptilolite, respect to the control group, not treated (14%); inferior body weight gain in the group treated with clinoptilolite (8%), respect to the control group (27%)	14
Effects of HSCAS and montmorillonite on aflatoxicosis	HSCAS 5 g/kg and montmorillonite 5 g/kg	Rats	Significant improvement of hematological and biochemical parameters (P<0.05)	17
Increase of bioaivalability of Si from zeolite, sodium aluminosilicate, magnesium aluminosilicate and aluminum hydroxide	Zeolite A 30 mg/kg, sodium aluminosilicate 16 mg/kg, magnesium aluminosilicate 20 mg/kg and aluminum hydroxyde 675 mg/kg	12 beagles dogs	Zeolite A significantly increased plasmatic Si (9.5 + 4.5 mg hr/L + SD; P=0.041)	18
Antioxidant and neuroprotective effects of clinoptilolite	Clinoptilolite 0.6 – 1.25 – 2.5 ng/ml for 5 months	Mice	Significant reduction of cellular death induced by ROS (P<0.001); significant reduction of ROS production in mitochondria (P<0.001); significant increase of the activity of SOD enzyme in the hippocampus of mice (P<0.001); significant reduction of the levels of amyloids plaques (P<0.05)	19
Effects of clinoptilolite on dichlorvos poisoning	Clinoptilolite 1 g/kg	Rats	Significant reduction of cholinesterase enzyme inhibition in different tissues investigated (P<0.01)	20
Effects of tuff-zeolite on VX poisoning	Tuff-zeolite 1 g/kg (61% clinoptilolite)	Rats	Significant reduction of cholinesterase enzyme inhibition in different tissues investigated (P<0.001)	21
Evaluation of carcinogen properties of clinoptilolite	Clinoptilite 0, 30, 60 mg	100 rats	Absence of a significant increase of tumor incidence in organs and tissues investigated	22
Evaluation of hemostatic properties of QuickClot (QC and ACS)	QC and ACS	32 Yorkshire pigs	Reduction of bleeding in groups treated with QuikClot devices (7.4% QC and 10.3% ACS), respect to the group treated with standard medications (22.3%); major increase of time death in groups treated with QuikClot devices (188 minutes QC and 194 minutes ACS), respect to the group treated with standard medications (96.8 minutes); increase of 4 hours global survival in groups treated with QuikClot devices (6/8; 75%) respect to the group treated with standard medications (1/8; 12.5%) (P<0.02)	23

Table III (cont.)
Experimental studies of zeolite

Application	*Zeolite concentrations*	*Sample*	*Results*	*Bibliography*
Inhibition of melanogenesis	Zeolite 4A 0.16-100 μg/ml	B16F10 melanoma cells	Reduction of melanogenesis (P<0.001)	24
Anti-diarrhea effects of clinoptilolite and modification of hematocrit levels, plasmatic fibrinogen and total proteins concentrations	Clinoptilolite 1.5% and 3% for 6 weeks	30 newborns lambs	Reduction of diarrhea gravity index (P<0.05)	25
Effects of diet supplementation with clinoptilolite	Clinoptilolite 0.5% and 1% for 45 days	200 chickens	Reduction of microbial gut infection (P<0.05); increase of the growth rate (P<0.05); increase of the body weight (P<0.05); increase of the level of n-3 polyunsatured fatty acids (P<0.05)	26
Effects of clinoptilolite on tumor cells inhibition	Clinoptilolite 85% for 24 hours	Mouse fibrosarcoma cells, small cells carcinoma, human pancreas carcinoma cells	The number of viable cells, the DNA synthesis, the activity of EGF-R, pKB/Akt and NFKB were significantly reduced (P<0.01)	27
Effects of clinoptilolite in improving the health status and in prevention of mycotoxins intoxication	Clinoptilolite 2% for 2 days and for 14 days	30 calves	serum plasma fibrinogen, total albumin, beta and gamma globulin were significantly higher after 14 days (P<0.05)	28
Effects of clinoptililolite on clinical ketosis	Clinoptilolite 1.25% and 2.5% for 4 weeks;	52 Holstein cows	significant reduction of ketosis (P<0.01) at both the clinoptilolite concentrations	29
Effects of clinoptilolite against aflatoxicosis	Clinoptilolite 15 g/kg for 42 days	576 broilers	the number of affected chickens and the organs degeneration were significantly inferior (P<0.05).	30

the reduction of $CD56^+$ cells. Any adverse event was registered.

A clinical investigation of Dr Ilse Triebnig in the oncological center of Villach (Austria) was conducted on 2000 oncological patients (personal communication; not published). Patients received a clinoptilolite medical device (MULTIZEO Med) according to different protocols of administration. An improvement of 100% of post-chemotherapy mucositis, a medium remission of 70-80% of gastritis, vomiting and diarrhea and a slight improvement of the blood count were verified. Consequently this medical device may be considered as a potential chemotherapy and radiotherapy coadjutant. The granular formulation was preferred, since it was administered through water, fruit juices, yogurts and others beverages.

A recent publication of Potgieter W et al.[32] investigated the effects of clinoptilolite in endoscopically negative gastroesophageal reflux disease (ENGORD). This was a randomized double-blind placebo-controlled study. 25 ENGORD patients received 750 mg of Absorbatox ™ 2.4 D clinoptilolite medical device or placebo, twice daily for 14 days. At the end of the study the severity of symptoms (according to the Sidney system) including reduction in heartburn, discomfort and pain was reduced respectively of 44%, 54% and 56% (P<0.05). The prevention of mucosal erosion severity probably was due to the bond between clinoptilolite with hydrogen ions end pepsin enzymes on the gastric mucosa. However amines and nitrates of clinoptilolite may reduce the damage on gastric mucosa.

Nakane T et al.[33] investigated the antimicrobial effect of an Ag-zeolite 5-40 w/w% formulation against axillary resistant bacteria. The compound was efficacious in neutralize skin bacteria for 24 hours involved in the production of decomposed and denatured metabolite compounds responsible of malodorous armpits. In this way Ag-zeolite may be a valid candidate in antiaxillary odour deodorant.

Table IV summarizes studies analyzed in this paragraph.

Conclusions

Although the progression of commercial zeolite devices, there is not a really clinical evidence of the efficacy of this compound. The adsorbent properties of cations, heavy metals, ammonium, toxins, etc. are quite stimulant in the environmental application of zeolite in order to remove pollutants from water, soil and foods. This review displays current scientific evidences about different fields of zeolite applications, and may serve as a support to other potentials experimental and clinical investigations.

The detoxificant role of zeolites is already evident in the agro industrial and in the zoothecnical fields. While the hospital diffusion as a potential coadjutant of toxic chemotherapy appears to be the most relevant clinical use of zeolite. However it is important to demonstrate that zeolite does not interfere with the absorption of chemotherapy drugs and does not reduce the bioaivalability.

Nowadays the detoxification attitude raises consents in many fields of medicine, from esthetic medicine to rehabilitative medicine. So, it is relevant to examine in depth the mechanisms of action of zeolite in order to confer to this device therapeutic properties. However others inert products, such as oral clays, bentonite and diosmectite, are already employed in the therapeutic fields such as in the treatment of irritable and colitis colon impairments. Clinoptilolite may be an additional compound effective in molecules removal. In this way it is very interesting to know its mechanism of action.

Instead it is nowadays unknown the control mechanism of local bleeding and of wound healing. Probably zeolite interfere with the corpuscle part of the blood and with the margins of wounds and wheals where it may interact with the hemostatic system, with cells of the margins of wounds and with the contraction of epithelial cells in order to provide the restitution ad-integrim. Arnaud F et al. showed that probably the absorption of water by zeolites is responsible of the concentration of platelets and clotting elements, displaying the formation of the clot[23]. Negatively charged surfaces of zeolite may initiate the blood coagulation cascade thanks to the concentration of blood coagulation factor in water absorption near to wounds.

Our aim is to develop a potential clinical application of zeolite and to provide a personal experience of employment.

Conflict of interest statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Statement of authorship

The authors hereby certify that all work contained in this article is original. The authors claim full responsibility for the contents of the article.

Table IV
Clinical studies of zeolite

Pathology	*Dose of zeolite*	*Sample*	*Study design*	*Results*	*References*
Immunosuppression	Megamin 3.6 g/day and Lycopenomin 1.2 g/day from 6 to 8 weeks	61 patients	Prospective and controlled open-labeled study	Significant increase of lymphocytes CD4+ and CD19+ (Megamin); significant reduction of lymphocytes CD56+ (Megamin); significant increase of lymphocytes CD3+ (Lycopenomin); significant reduction of lymphocytes CD56+ (Lycopenomin); absence of side effects	31
Cancer	MULTIZEO Med	2000 patients	N.d.	Improvement of 100% of post-chemotherapy mucositis; medium remission of 70-80% of gastritis, diarrhea and vomiting; improvement of blood count values	Personal communication; not published
ENGORD	Absorbatox™ 2.4 D	25 patients	Randomized double-bind, placebo-controlled study	Significant reduction in severity of heartburn (44%), discomfort (54%) and pain (56%) ($P<0.05$)	32

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