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Synopsis

"The Boiling Stones": Prospective and Reliable Biodetoxicators

Roumiana P. Metcheva**, *Michaela N. Betcheva, Peter V. Ostoich

Institute of Biodiversity and Ecosystem Research - Bulgarian Academy of Sciences,
1 Tsar Osvoboditel blvd., Sofia 1000, BULGARIA
*Corresponding author: rummech@yahoo.com

Abstract. Zeolite is a collective name for minerals and chemical compounds within the group of aluminium silicates. Clinoptilolite is one of the members of the zeolite family and is the most widely used natural zeolite in different studies. Nowadays nature is increasingly exposed to toxic elements, pesticides, and different kind of anthropogenic pollutants. This leads to health problems like decreased immunity, allergies, respiratory disorders, cancer, etc. Zeolites are beneficial in many fields because of their grid structure and chelation-like effect in removing heavy metals. Over the last decades numerous studies with clinoptilolite were performed in both humans and animals. The basis of interest is its biological effects concerns one or more of their physical and chemical properties. In medicine, especially micronized natural zeolite-clinoptilolite is a relatively novel subject of interest. Animal studies demonstrate that zeolites show great promise for environmental protection, capability to detoxication of animal and human organisms, improvement of the nutrition status and immunity of farm animals, separation of various biomolecules and cells, and strong antioxidant activity. There is a significant detoxifying effect after clinoptilolite supplementation in the animal diet because of its ion exchange capacity and effective enterosorption for heavy metals, radionuclides and other inorganic pollutants. Recent findings indicate that clinoptilolite applied orally in laboratory mice for 90 days provides direct detoxification and shows significant and effective reduction of lead accumulation. Further research is needed to explore the effects of a zeolite-clinoptilolite to clarify the role of its detoxification mechanisms and auto-bioregulation in human and animal organisms.

Key words: Zeolite, clinoptilolite, enterosorbent, detoxication, mice.

Zeolite is a mineral occurring naturally in rocks of volcanic origin, formed millennia ago. The volcanic ash was deposited into an alkaline water source and was put under pressure where it reacted and crystallized. Zeolites are usually formed as secondary minerals and form beautiful crystals with pale colors. They are relatively soft and can be crushed and powdered. It is a collective name for minerals and chemical compounds within the group of the hydrated alumino-silicates. Zeolites have large anions containing cavities and channels. They rarely are pure and may contain all of the elements of the periodic table in varying degrees (Hay & Sheppard, 2001).

In prehistoric cultures, various minerals have been widely used and taken as food, as do many animals in nature. There even exists a special term – lithophagy. Surprisingly, when scientists decided to study what kind of stones are licked by animals in the spring, it turned out that these stones were exactly zeolites. Numerous observations prove the existence of lithophagy. Moose, deer and wolves find stones and lick them as an integral part of their vital needs (Panichev, 1989, 2015, 2016). It was thought that animals were seeking salt in nature to compensate their sodium deficiency. It has been found that the stones they select have nothing to do with salt. Studies show that ion exchange processes take place between animals and stones. The organism is released from unnecessary and harmful substances and fills in the missing ones. One of the hypotheses for lithophagy is an instinct for self-healing. Lithophagy is widespread also in monkeys, and even in humans to restore normal exchange in the body (Panichev & Golokhvast,2011; Panichev et al., 2013).

The term "zeolite" was originally introduced in the 18th century (1756) by the Swedish mineralogist Baron Axel Cronstedt. He discovered that when the mineral was heated rapidly a large amount of steam was obtained and named it "zeolite". The name originates from the Greek ζέω + λiθος. "Zeo", meanis to boil and "lithos" means rock (stone). Zeolites swell when heated strongly and quickly, forming a bubble glass. Zeolite is a name applied to a huge number of extremely porous natural minerals mined in a number of locations worldwide.

For almost two centuries, no one was interested in zeolites and they gained new popularity only at the end of the 20th and in the 21st century.

It was found that the zeolite rock is almost monomineralic and consists of clinoptilolite (CLN). It is the most widely used zeolite. It has been declared the mineral of the 20^{th} century by the World Scientific Organization and became extremely popular due to its exceptional qualities. There are numerous fields of application of natural zeolites, especially clinoptilolite, which can act as medicines (Rodriguez et al., 2006; Pavelic et al., 2001), as concomitant therapy (adjutants) (Auerbach et al. 2003), as a carrier for catalysts and pharmaceuticals (Cerria et al., 2004, Hernandez et al., 2016), in the food industry, agriculture, astronautics, and in different fundamental and applied research concerning animals (Mumpton, 1999; Pavelić et al., 2001).

What makes zeolites so unique?

Zeolites contain water in the spaces between the Al and Si molecules (tetrahedra). This water moves easily in and out of the crystal. Consequently, any molecule similar in size to water or smaller can pass through the zeolites' spaces. Larger molecules, however, cannot. Zeolites are therefore used as molecular sieves or filters to remove molecules of a particular size. Liquids and gases can pass through these spaces or pores. This property is utilized in a wide variety of applications (Breck, 1974).

The structure is the basis of the extraordinary qualities of these minerals. All zeolites have three-dimensional crystal structures enveloping an internal surface available for adsorption because of the same-sized channels with irregular shape and cavities with uniform pores of molecular size, which are uniformly distributed throughout the volume. This structure contributes to the minerals' superior ion exchange and adsorption properties (Petrov & Michalev, 2012). Cations and water molecules are weakly bound to the framework and can be partially or completely removed by ion exchange and dehydration. It is proven that zeolite is multifunctional and has important properties: sorption, molecular sieving, ion exchange and catalytic properties (Vorotnikova et al., 2020). These minerals are microporous, commonly used as adsorbents and catalysts. The most interesting property of zeolites is their open, cage-like honeycomb structure, negatively-charged. Most heavy metals are positively-charged. Like a magnet, zeolite attracts and then traps those heavy metals inside its structure. It's a process called cationic exchange. Zeolites have regular openings with fixed size, which lets small molecules pass straight through but traps larger ones; that's why they're sometimes referred to as molecular sieves.

The properties of zeolite are determined mainly by their structures. Therefore, it is important to know how to explore, utilise and use them for new applications.

What are zeolites used for?

Because of their cage-like structure large adsorption surface and unique physical and chemical properties *zeolites are* important materials with overly broad applications:

- Used as molecular sieves where they can retain molecules that can fit into their molecular cavities; have high cation exchange capacity for heavy metal cations which can be exchanged with other ions;

- Molecules or ions larger than the pore opening of zeolite cannot be adsorbed, smaller molecules or ions can;

- Useful for a variety of environmental remediation processes;

Besides, clinoptilolite effectively removed harmful toxins, many studies have shown that they also have many other vital effects in the body;

- Natural zeolite has diverse biological activities by trapping and slowly releasing valuable nutrients;

- It is used as an Additive in concentrated feed in animal growing facilities to improve feed conversion;

- Zeolite first removes free radicals. Unlike classical antioxidants, clinoptilolites do not neutralize free radicals by transferring an electron to stabilize them, but instead trap the free radicals. Once in the cell, free radicals are inactivated and can thus be safely eliminated from the body;

- Zeolites have a wide range of antiviral properties: first, by attracting and binding viral subparticles, thus preventing viral replication and their elimination from the body, and second, by inhibiting viral proliferation by immune modulation of T-cells;

- Zeolite helps maintain proper pH by removing acid ions and chemicals, which then improves optimal metabolism and immune function;

- Zeolites possess an antitumor effect. They help the elimination of carcinogenic toxins from the body, especially in the category of carcinogens called nitrosamines. They are most common in processed meats, cigarettes and beer, and have been linked to cancers of the pancreas, stomach and colon.

Zeolite deposits in Bulgaria

Alexiev (1968) is recognized as the pioneer discoverer of zeolite raw material and deposits (in quantities amounting to billions of tons) in Bulgaria.

Geological studies have been defined - the largest deposits of zeolites are located in the Eastern Rhodopes - around Kardzhali - " Zhelezni Vrata", the village of Beli Plast, "Beli Bair", "Golo Bardo", "Lyaskovets", etc. presented on Figure 1. The clinoptilolitic rocks in the North Eastern Rhodopes are of potential industrial significance because of their widespread distribution, high clinoptilolite content, considerable thickness of the layers (Djourova et al., 1989; Djourova & Milakovska-Vergilova, 1996).

The oldest deposits are in Australia, but the Bulgarian ones are many times better and amount to 10 billion tons. 60 deposits have been discovered in Russia. Their amounts are only 3.5 billion tons, as many as there are only around the vicinity of Kardzhali.

So far, more than 40 types of natural zeolites are known, the most common of which is clinoptilolite (CLN).

It was found that the zeolite from the deposit near Beli Plast is almost monomineralic and consists practically of pure clinoptilolite. It contains nearly 85 wt. % CLN and opal-CT ~15 wt.%.

Its percentage chemical composition is:

SiO_2 - 62.74%; **Al_2O_3** - 9.68%; **Fe_2O_3** - 0.74%; **CaO** - 6.73%; **MgO** -2.9%; **MnO** - 0.03%; **SO_3** -<0.03%; **TiO_2**- 0.12%; **Na_2O** - 0.29%; **K_2O** - 2.79%; **H_2O** - 5.00%; **3H**- 13.74%

and its chemical formula - $(Ca,Na,K)_{2-3}.Al_3\,(Al,Si)2Si_{13}O_{36}.12(H_2O)7O$-7

The range of concentrations of the trace elements reveal very low contents of the consistent elements (as Ni, Cr, Co, Sc, Eu^{2+})

which are often below the limits of detection (Rajnov et al., 1997).

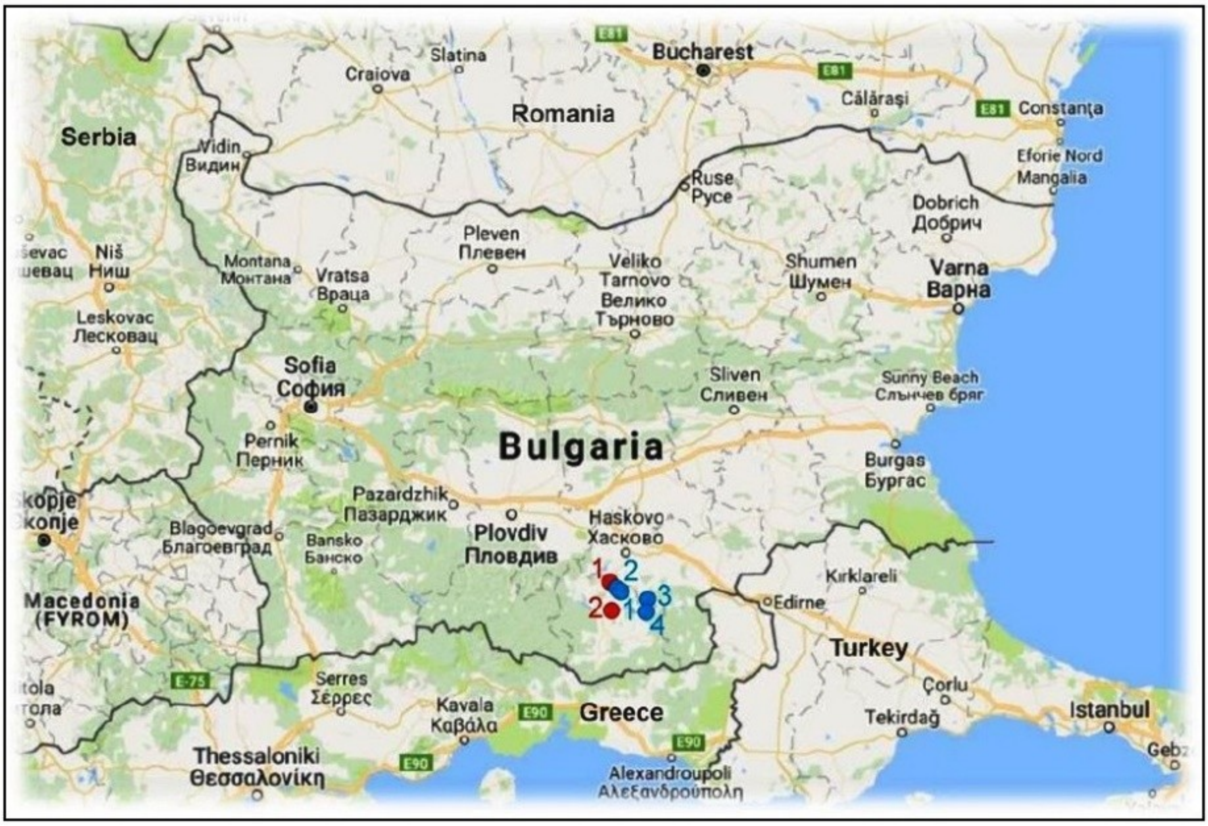

Fig. 1. Indicative map of distribution of natural clinoptilolites in Bulgaria.
Exploited deposits: ❶ - Beli Plast, ❷ - Belia Bair – Zhelezni vrata,
Explored deposits: ❶ - Most, ❷ - Gorna Krepost, ❸ - Lyaskovetz, ❹ – Golobradovo.

In order to better understand the mechanism of binding different toxic elements, it has to be mentioned that zeolites are naturally occurring chelators in removing toxic agents and the prevention of poisoning. Chelators are substances used to separate metal ions from solutions or other mixtures. They have two or more binding sites that bind particular ions and build very stable complexes.

Upon ingestion, a chelator attracts and irreversibly binds heavy metals, chemical elements and free radicals, after which it is excreted through the urinary and digestive tracts. This process is called chelation. The name "chelate" comes from the Greek "chela" - "nail, clippers".

The metal ion is captured by the chelator and thus becomes the central atom of the complex. Thus, the chelate prevents toxicity of some heavy metals (Williams & Halstead, 1982).

One of the most significant advantages of CLN over other chelating agents is its specific affinity for toxic elements and heavy metals. CLN binds first Hg, then, Pb, Cd, As, Al, Ni etc. It is ability to attract and trap them gives it such powerful detoxifying potential.

The ppropertiеs of CLN are essential for the adsorbing characteristics due to the exceptional exchange capacity, as well as the surface area. Thanks to activation technology its sorbing capacities increase. CLN, in general, is known as an environmental decontaminant and has multiple application in the last 20 years.

Studies performed over the last decades show the high potency of zeolites - CLN in diverse medical applications *in vitro* and *in vivo*. In medicine, especially micronized natural zeolite-clinoptilolite is a relatively novel subject of interest.

The unique properties of zeolites were characterized using gravimetric analysis and have been subjected to chemical, microscopic, X-ray fluorescence, powder X-ray diffraction, Fourier transform infrared (FT-IR) spectroscopy, differential thermal analyses and thermophysical evaluation.

Not all types of zeolites are safe to be used. The clinoptilolites from different regions show different behaviour in ion-exchange processes. They possess unique chemistry, specific for each of the species. Because of how they are formed, naturally occurring zeolites are rarely found in pure form. They are often contaminated in varying degrees of metals, quartz or clays. Even CLN natural tuffs contain small quantities of different trace elements, and always are pre-loaded with various cations.

In particular, it has been found that the zeolite erionite is associated with lung cancer and malignant mesothelioma because of containing toxic fibres (Giordani at al., 2017).

Zeolites are often contaminated by other minerals. This makes them extremely important to the type of their application. Theirs porous, honeycomb like molecular structure allows them to accommodate and assist in the exchange of cations such as: Rb^{+}, Na^{+}, Ba^{2+}, Mg^{2+}, Li^{+}, Ag^{+}, Sr^{2+}, Fe^{3+}, K^{+}, Cd^{2+}, Cu^{2+}, Co^{3+}, Cs^{+}, Pb^{2+}, Ca^{2+}, Al^{3+}, NH^{4+}, Zn^{2+}, Hg^{2+}, Cr^{3+} and many others.

But a zeolite that is already full of metals does ***not*** work. It's like a sponge that's already wet; it won't absorb any more water. When using 'un-cleaned' zeolites a high level of Pb, Cd, As and other metals will come out.

For zeolite to trap toxins in the organism, it must first be cleaned of its ***existing*** heavy metals. It has been tested and confirmed and it is the ***only*** way to know what is inside.

The **cage-like structure of zeolites** makes them useful in many ways and sustainable applications for heavy metals detox, alcohol detox, toxins detox, gut health, oxidative damage reduction, mitigation of environmental toxins, detoxication against radioactive materials, counteracting microbial pathogens. In the 1960's, zeolites were given as bio additives to astronauts during long flights.

Zeolites have proven extremely effective at removing radioactive particles from nuclear waste and cleaning up soils contaminated with toxic elements (Lee et al., 2017). During the Chernobyl disaster, specialists secured the site with zeolite powder in order to bind the radioactive isotopes ^{90}Sr, ^{134}Cs and ^{137}Cs, and thus reduce their content and neutralize radiation. Zeolite was effective in removing for the first three months (Voitsekhovitch et al., 1997, Chelishchev, 1995). Following the Fukushima nuclear disaster in Japan in 2011 five types of zeolites were tested (Johan et al 2015). On paddy fields zeolites were spread an attempt to trap any lingering radioactive contaminants (Wakahara et al., 2014).

Natural clinoptilolite has to be activated in order to be applied as a detoxifier.

Bulgarian scientists from the Institute for Applied Research of Mineralogy BAS (Djurova et al., 1989) found that under normal conditions, the CLN charge is pretty weak. This small disadvantage required the need to find a reliable formula to activate it. Popov et al., (1997, 2012), Ivanova et al., (2001) have merit in this respect. Finding an exact formula for activation proved challenging and unexpected difficulties and took about seven years of experimentation, trial and error. Of great importance is the type of CLN and its pre-treatment. The activation is possible after chemical treatment with acid or alkaline solution replacing stabilizing cations in dry or in liquid medium. Another way is to heat the material or to apply mechanical modifications, even micronization in order to increase the surface area, pore size and the adsorption capacity. These treatments allow the removal of impurities (some exchangeable cations located in the channels could be trapped), to enhance the sorption properties, surface area, and porosity (Abdulkerim, 2012; Akimkhan, 2012; Canli & Abali, 2016).

The CLN structure is still stabile after 12 h of heating at 750°C, whereas other zeolites' structures are destroyed after 12 h at 450°C (Ghiara et al., 1999). This structural stability is an essential element for *in vivo* applications. Thus, the specific sorption capacity can be significantly increased and can reach up to 100 mg/g sorption for heavy metals and radioactive substances.

The size of the zeolite surface area is important

1- Zeolite works like a sponge and that allows to soak water. Cutting the sponge in half it becomes double reached the number of cells available to soak up water. If cut again the number of cells will quadrupled. Reducing the size to an average of 0.3 μ gives a much larger surface area and ability to remove toxins.
2- Zeolite particles larger than 0.3 μ are not able to enter the bloodstream than they stay in the colon where the exposure to toxins in some degree limited to removal. For example, strong toxins are usually accumulated in the fatty tissues.
3- The only way to safely remove toxins from the fatty tissues is to ensure that the zeolite can reach them via the blood stream. The way for detoxication is only when zeolite come to physical contact with the toxins or heavy metals for the ion exchange to occur.
4- The larger size of particles remains in colon and help it to cleanse as well.

Are there any side effects from the application of different concentrations of natural zeolite - clinoptilolite *in vivo?*

Blagoeva et al. (1999) provided two-year observations on laboratory mice and rats, which daily consumed food supplemented with 5% CLN. The authors did not establish any effect on basic biological parameters in animals – body weight and survival. No toxic effects were observed on the lungs, heart, spleen and kidneys. After 70 days of oral treatment with food containing 20% CLN there were no visible changes in the digestive tract and no clastogenic effect was observed in the bone marrow cells, nor any changes in peripheral blood parameters.

All conducted experimental studies strongly confirm the complete harmlessness of CLN when fed as a food additive in a concentration of 1 to 6% (Vinichenko, 2011; Gamko, 2012, Phenchenco et al., 2002).

The first comprehensive acute, sub-chronic, and chronic toxicology evaluation of CLN material *in vivo* was performed by Pavelić et al. (2001).

The only zeolite used for medical purposes in animals and humans so far is the natural zeolite - clinoptilolite, because its basic structure is considered to be biologically neutral and non-toxic (Auerbach et al., 2003).

2013 EFSA (European Food Safety Authority) evaluated and demonstrated that non-toxic doses of CLN given to animals have to be up to 10000 mg/kg.

Detoxification **s**tudies performed in the last decades demonstrated a high potency of CLN in diverse medical applications *in vitro* and *in vivo* (Kraljević-Pavelić et al., 2018). They presented the positive effect of CLN due to reversible ion-exchange and adsorption capacity (Mumpton, 1999; Pavelić et al., 2001; Jurkić et al., 2013). This basic CLN characteristic related to elimination of toxic agents, which may be seen as a support to the 'body homeostasis,' could be widely exploited in a severalmedical applications. Ortatatly & Oguz (2001) demonstrated the effects due to the CLN capacity to absorb harmful substances in the gastrointestinal tract.

Animal studies show that CLN demonstrates great promise for environment protection. Its capability for detoxification of animal organism, improvement of the nutrition status and immunity of farm animals, separation of various biomolecules and cells, strong antioxidant activity is remarkable (Pavelic et al., 2001; 2002).

Environment decontamination from different toxins and organic pollution derived from industrial waste is essential for biological ecosystems. Due to its binding capacities, CLN has been generally used in the zootechnical field for water purification and remediation.

Environmental contaminants accumulate throughout the food chain. For this reason, CLN is studied and used for oral supplementation to bind toxic substances such as ammonia or heavy metals in the milieu of the gastro-intestinal tract.

That is why the new term "enterosorbent" was introduced for substances in the digestive tract that bind and neutralize toxins or harmful products (Zhuchkov et al., 2011).

Using the CLN as an enterosorbent contributes to the improvement of livestock and poultry health and increasing their productivity. This process is due to the adsorption of trace elements, creating a certain reserve, which is used by the body evenly for a long time. The concentration of mineral elements in the digestive tract is maintained at the optimum level which improves the overall physiological state of animals. The selective ability of CLN to adsorb NH_4^+ ions in the gastrointestinal tract also contributes to higher productivity. Cations of Mg, Mn, Zn and other elements stimulate the protein synthesis and this leads to increase in the productivity of livestock (Ulitko, 2003; Mysik, 2012; Osinkina, 2012).

Clinoptilolite incorporated into the diet may be effective enough in fighting toxins by direct absorption. CLN has strong chelating ability, which is potential for adsorbing toxic metal cations, especially Pb.

CLN only "passes through" and never goes into the bloodstream. Affinity was proven by dietary administration of 5% CLN in mice, in the presence of amino acids and vitamins. It is very important to know that they will be not absorbed by the CLN material, especially in the smallest particle size.

A lot of *in vivo* studies on the detoxification properties of CLN performed so far have mainly been done on animals and they provide strong evidence on alleviating effects during exposure to different toxicants upon CLN supplementation (Laurino & Palmieri, 2015).

Our research have shown that CLN provides direct detoxifying performance in ICR laboratory mice. For instance, in lead-intoxicated mice, a CLN sorbent KLS-10-MA decreased the lead accumulation in the intestine by more than 70% (Beltcheva et al., 2012, 2015). During the detoxification processes the performed morphological, cell and genetic analysis shows normalization of the physiology of the animals' organism. Prolonged use of CLN has a stimulating effect on the biosynthetic processes (Topashka-Ancheva et al., 2011).

Conclusions

This brief review exemplified the orientation and necessity of research in the field of modern ecotoxicology combined with new approaches s and advanced methodology of exploration.

The efficacy and potential of CLN in medicine seems high. In the organism the possible effects of CLN administration on different micronutrients and trace elements, or on important physiological processes does not affect their homeostasis, but acts rather selectively on heavy-metals and toxicants.

The majority of studies on CLN were done by using different, so-called activated materials to increase either the surface area or to improve the CLN general adsorption or the ion-exchange capacity.

The tested CLN materials proved to be generally safe for (*in vivo*) applications even though each CLN seems to have its own characteristics and demonstrate specific biological effects. That cannot be easy to explain because a great part of mechanisms is not exactly clear and is still not completely understood. The difficulties come from different particle sizes, surface areas, and cation compositions that may induce different biological effects and exert different levels of effectiveness. Biological effects and toxicology data should be carefully evaluated according to the type of CLN used in a particular study or application.

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