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Review Article

Potential Role of Zeolites in Rehabilitation of Cancer Patients

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1. Summary

Recent data indicate the beneficial effects of modified natural zeolite. One of them is clinoptilolite registered as a medical device for human use (e.g. zeolite-PMA-Panaceo Micro Activation). It can be used in the treatment and rehabilitation of patients with various diseases, such as bone and joint and cancer. Data reported in the scientific literature undoubtedly indicate the potential beneficial effect of zeolites on the course of the disease following aggressive therapy. Due to their specific physicochemical properties, natural zeolites could be very useful in the rehabilitation of patients treated for malignant tumors. These properties are detoxification, antioxidative effect, immunostimulation, histamine binding and direct effect on tumors. Those properties are all related to the rehabilitation of cancer patients undergo aggressive anticacer therapy. Here we present the scientific facts that support this thesis. The natural zeolite-clinoptilolite is an aluminosilicate mineral of volcanic origin [1] built of silicon (SiO_4) and aluminium (AlO_4) tetrahedra connected to each other sharing one or more oxygen atoms. These group of crystals have a framework with intra-crystalline cavities and channels important for their properties as these contain water, polar molecules or ions which are exchangeable. The propertires of cation-exchange and adsorption are indeed, the main properties that make the natural zeolite-clinoptilolite probably the most important inorganic cation exchanger, particularly in industrial applications [2]. Some well-described ion

exchange or adsorption properties of zeolite-clinoptilolite are for heavy metals and cations lead (Pb), cadmium (Cd), arsenic (As), chromate (Cr), nickel (Ni) and ammonium (NH_4^+) and as well as for aluminium (Al) [3-5]. Based on the ion-exchange capacity the zeolite-clinoptilolite is used in many industrial sectors [6, 7] and veterinary or human medicine [5, 8]. Especially the research or application of zeolite-clinoptilolite as adjuvants to standard therapies in human medicine is a growing field because of its antioxidant effect [9], hemostatic [2] or anti-diarrheic properties [10] or immunmodulatory effects [11] as well as detoxification, release of trace elements or positive influence on the intestinal microbiota [12]. Already few clinical studies prove the positive impact of a specific zeolite-clinoptilolite on the integrity of the intestinal barrier, decreasing the concentrations of zonulin and showing furhtermore a positive impact on compliants in the gastrointestinal tract such as improvement of nausea and diarrhea [13].

The positive impact on interleukin-10 which was also observed in the study of Lamprecht et al. [13] can be seen as an action on the intestinal lymphoid tissues and was also observed in the metabolites released by probiotics capable of improving the intestinal ecosystem and boosting the immune system [14, 15]. When it comes however to the application of zeolite-clinoptilolite in medicine it must be ensured that the mineral source used for preparation of the material for *in vivo* applications is safe. From a medical point of view, it is essential to use only those zeolite products for a safe human application that are certified medical devices and therefore have the appropriate homogeneity and quality. According to recently published reviews one possible material for this kind of medical applications is the PMA-Panaceo Micro Activation-zeolite clinoptilolite [5]. Recent papers show a differentation of properties related to specific tribomechanical activation processes [16, 5]. However, chemical structure of this material underly the stability of tested clinoptoilolite materials as clinoptilolite has been scientifically and widely recognized as a highly stable alumosilicate structure both at increased temperatures and different extreme pH solutions (pH 2–11). The conditions in the human intestine ranges from 1.5 (fasten) – 3.5 in the stomach to approximately 6 in the duodenum towards 7 in the distal part of small intestine. The collapse structure starts only above 400°C and occurs between 600-900°C [17]. This means the thermal stability is wide above the physiological temperatures of the human organism (approximately 37°C).

Clinoptilolite-based materials, including PMA-Panaceo Micro Activation-zeolite clinoptilolite have been tested in vivo on animals and humans showing a panel of interesting biological applications that might be interesting while evaluation possible adjuvant effects in certain medical conditions., i.e. cancer. Indeed, most patients with malignant tumors undergo severe chemotherapy, radiotherapy, and / or surgery that require rehabilitation and elimination or reduction of adverse effects after therapy. Such treatments can produce severe side effects due to their negative effects on the organism. Chemotherapy and radiotherapy in particular can have negative effects at intensively dividing cells, due to the release of free radicals, immunosuppression, as result of the adverse effects of products released by such therapies. Thus, antitumor therapy can ultimately produce serious adverse effects if not prevented. Considering the physicochemical

properties of zeolites, we propose that these materials might help rehabilitation, i.e. faster recovery of cancer patients after complex therapeutic interventions. Studies reported on zeoliters mainly refer to experimental models. Recently, a number of controlled clinical studies have been conducted in humans to demonstrate the safety of paricular zeolite clinoptilolite [18] and the positive effect on neuropathic pain after undergoing chemotherapy (personalcommunication, in preparation).

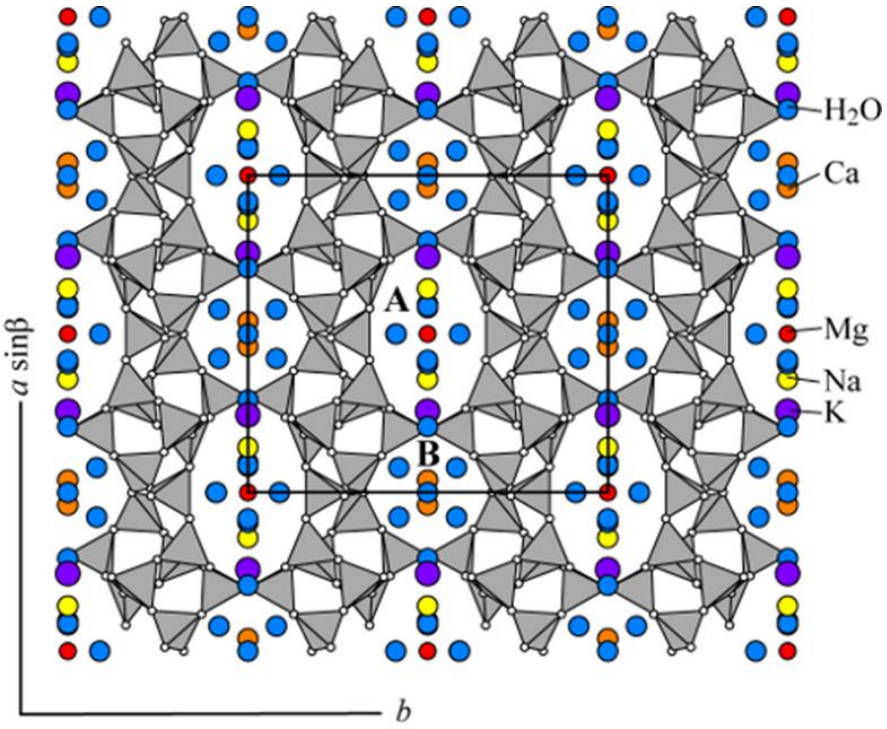

Figure 1: Clinoptilolite crystal structure representation - hydrated sodium potassium calcium aluminum silicate. Typically clinoptilolite contains 4 to 7 cations per unit cell (adopted from Internatioanl zeolite association website: http://www.iza-online.org, accessed on 24th February 2020).

2. Detoxification

One of the best known effects of zeolites is detoxification which is extremely important for the elimination of harmful substances from the body as well as from the environment. Two properties of zeolites are important for detoxification: ion exchange and adsorption capacity. Due to this, zeolites effectively adsorb heavy metals such as lead, aluminum, arsenic, cadmium and ammonia [19] as well as toxic products such as phenols, pesticides, mycotoxins [20, 21]. These factors can increase the concentration of free radicals in the body [22] which can damage the organs including brain, liver, kidneys and intestines. Zeolites neutralize free radicals by trapping them within their complex structure which then chemically inactivates them (Figure 2). The special role of zeolites in the detoxification of patients could be in preventing the neurotoxicity caused by chemotherapeutics or other

symptoms of different pathologies due to increased oxidative stress (Figure 3). This is relevant as some of the effects of the toxins may be on nerve cells where they lead to depletion of intrinsic antioxidate defenses, destabilization of calcium homeostasis, damage to electron transposts, ATP depletion, and membrane channel ion disruption, which all lead to apoptosis. The major exchangeable ions in the zeolite clinoptilolite are the physiological minerals sodium, calcium, magnesium or potasium [23]. The preloaded material may be seen as a guarantee that *in vivo* applications of this highly reactive material will not act as a potential ion-robber in the intestine but will rather release physiological cations by a simultaneous uptake of contaminants from the environment.

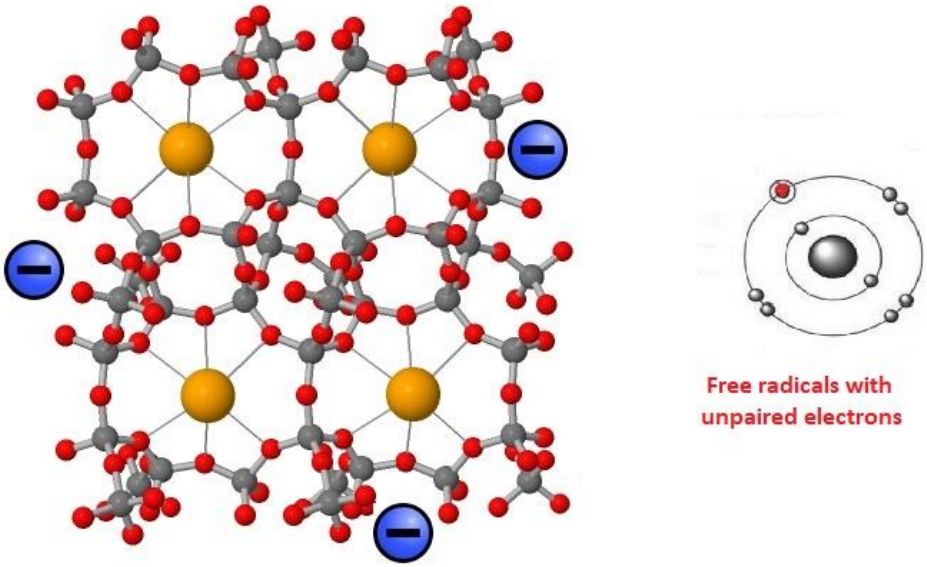

Figure 2: Negatively charge clinoptilolite structure may neutralize the free radicals. The presented clinoptilolite structure has been used from the chemtube3d.com source.

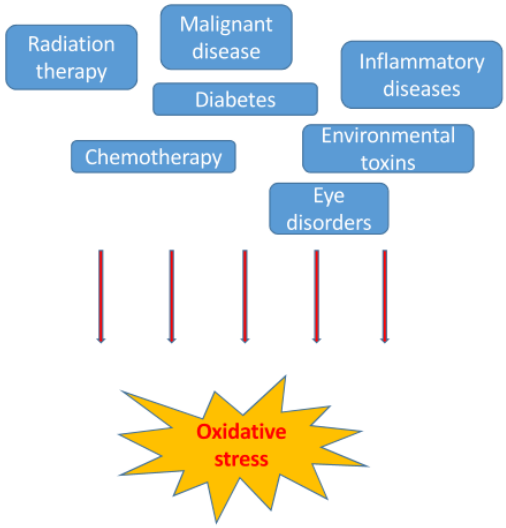

Figure 3: Potential applications of clinoptilolite-materials in different pathological states that induce oxidative stress.

3. Antioxidative Effect

Oxidation is a chemical process characterized by the loss of an electron in a molecule, atom or ion that leads to an unstable state. The resulting electronic configuration of the so-called free radicals are responsible for their reactivity. Free radicals act as electron robbers from other molecules that they come into contact with. These molecules then also become free reaction radicals that capture various biological molecules, including nucleic acids, lipids and proteins. Any change in proteins can be correlated with, for example, alteration of the enzymatic activity of DNA transcription factors or make the proteins prone to degradation. An endogenous source of free radicals includes environmental pollutants, UV light, drugs, heavy metals and certain chemicals such as pesticides. The production of free radicals can be induced by xenobiotics and drugs, as mentioned above, with the result of oxidative stress and tissue damage [24]. These are, for example, chemotherapy agents or radiation primarily used in the treatment of cancer patients, or even some viral diseases. Unfortunately, the administration of these drugs causes a number of unwanted changes, such as damage to cells and tissues that are otherwise not even affected by the primary disease, then drug resistance, necrotic apoptotic cells, which then promote the inflammatory response also to neighboring cells. Since the disparity between reactive oxigene species and the antioxidant capacity of the body induces oxidative stress, the role of antioxidant mechanisms and the level of antioxidants in the body is crucial for maintaining health. Oxidative or reactive radicals can control many steps in signal transduction and regulation of gene expression. Many well-known pharmaceutical and biotechnology companies are trying to develop products that control redox processes in cells and organisms and help cure disease and even prevent aging [25]. One such product is zeolite - clinoptilolite.

Therefore, antioxidants are crucial for the defense of the body against oxidative stress that can be triggered by various external factors. Antioxidants can thus prevent damage to normal cells as well as drug resistance [26]. If the right concentration of oxidants and antioxidants is used, the antioxidant capacity of the cells can be enhanced. Moreover, the use of antioxidants can enhance the therapeutic effects of radiotherapy and chemotherapy [27].

In Žarković's publication [28] it is demonstrated that zeolites, especially clinoptilolite, have antioxidant capacity. It is also demonstrated that clinoptilolite induces lipid peroxidation as well as free radical levels in the gut thus increasing the overall antioxidant status in the serum. In clinical studies in humans, the chabazite / philipsite / analcine zeolite material has been tested for its effect on the antioxidant enzymes glutathione peroxidase, superoxide dismutase and reductase. The activity of all these antioxidant enzymes increased after 4 weeks of zeolite supplementation and the main indicator of oxidative stress - lipid peroxidation, was also reduced in healthy subjects included in the study, especially in smokers [29]. The antioxidant effect of zeolite has not yet been fully elucidated, since it is not orally absorbed in the blood after being taken. The *in vivo* effect of zeolite could be due to indirect and local interaction within the intestinal biochemical system such as through the removal of toxins and biological waste, activation of the immune system, through mucosal intestinal lymphoid tissue, and also by increasing the bioavailability of essential elements that are important cofactors for enzymes. It is also known that natural or artificial zeolites as components of food increase the activity of the antioxidant enzymes glutathione peroxidase, catalase and superoxide dismutase in the liver of treated chickens. Zeolite alone or in combination with other antioxidants such as vitamins from plant extracts can potentially protect the body against cytotoxic substances, chronic ethanol-intoxication, mutagens and / or carcinogens, aging, immunosuppression and environmental pollutants.

4. Immunostimulation

Experiments in animals and some clinical studies have demonstrated the role of clinoptilolite in modulating the immune response. Zeolites can stimulate the immune response in both humans and animals. Thus, ip inoculated zeolite microparticles have been shown to promote peritoneal macrophages [30]. Another study also shows an immunostimulatory effect, an increase in phagocytic activity of iron deposits in liver Kupffer cells in iron-treated mice [31]. Gastric intubation of clinoptilolite provokes a larger allogeneic graft-versus-host response. After ip inoculation, production of superoxide anion is increased and an increased and translocation of p65 (NFκB subunit) to the nucleus of splenic cells was observed. This suggests that clinoptilolite induces a local inflammatory reaction which is also observed with other silicate materials [32]. This causes the attraction of peritoneal macrophages at the site and their release of TNFα that stimulates T-cells. NFκB also acts as a regulator of targeted genes that induces T-cell activation, and this type of positive regulatory loop can amplify and perpetuate the observed local inflammatory response, which has an immunostimulated outcome [30, 33].

Another mechanism that clinoptilolite exerts is an immunostimulatory effect by induction of IgA [5, 16]. Chabazite treatment has already been shown to increase the production of B-lymphocytes and immunoglobulin

A with the consequent onset of IgA [34]. IgA is present on the surface of the mucous membranes where the first line of defense has acted. It is also known to mediate the organism's immune response to the microbiome of the intestinal flora. Moreover, in humans, a study with immunocompromised patients showed that supplementation by clinoptilolite increases the levels of CD4 + and CD 19+ and blood lymphocyte counts over a period of 6 to 8 weeks [11].

5. Histamine Binding

Some authors provide unambiguous evidence that zeolites can bind histamine and serotonin in the gastrointestinal tract, thereby reducing the negative effects of exogenous factors such as alcohol and aggressive drugs [35]. Therefore, the property of zeolite to bind histamine can be used not only to eliminate the negative symptoms of alcohol consumption but also other problems such as the negative effects of chemotherapy and radiotherapy in cancer patients. Histamine (2- / 4-imidazolyl / ethylamine) is a biogenic amine and a potent mediator of numerous biological reactions, including histamine intolerance [36].

Histamine plays an important role in controlling biological processes in humans such as allergic inflammation and the immune response. The major metabolic degradation pathway of histamine goes via the diamine oxidase (DAO) system, which controls ingested histamine from food. If DAO dysfunction occurs, histamine builds up in the body, which can cause painful reactions such as headache, pruritus or even diarrhea. We must bear in mind that histamine binding by zeolites can only occur in the gastrointestinal tract or at the site of topical zeolite applications.

6. Drug Interaction

The question arises of the interaction of drugs with zeolites. Various zeolites, including those with modified surfaces, have been tested for their possible interaction with small molecules or as drug delivery systems. It was also investigated whether zeolites could be co-administered with drugs without affecting the pharmacological actions of these drugs. For example, the interaction of clinoptilolite with two drugs - metronidazole and sulfometoxazole - was investigated. Oral administration of these drugs can cause side effects, mainly associated with indigestion. Four types of zeolites were tested in different pH conditions: natural untreated material, purified (washed with distilled water) and zeolites enriched with calcium or sodium. An important finding of the study was that these and other organic drugs showed no signs of degradation after contact with zeolites regardless of pH conditions. These and other data undoubtedly indicate that the simultaneous administration of the tested drugs with zeolites will not affect the individual pharmacological properties of the drugs. In the aforementioned studies, it is clear that the adsorptive properties of zeolites towards drugs are dependent on the molecular polarity of the molecule and on the type of material [37]. Similarly, the adsorption and desorption of aspirin on the surface of clinoptilolite under acidic conditions is relevant to human intestines. *In vitro* data have shown that aspirin can be co-administered with zeolite since it is highly adsorbed in the acidic gastric conditions and desorbed in the lower pH conditions of the intestine. The concomitant effect of clinoptilolite and the anticancer drug doxorubicin *in vivo* was also monitored. The joint treatment of these two preparations resulted in a strong reduction of pulmonary metastases and an increase in the anticancer

effect of doxorubicin. Recently, advanced thermal pH responsive zeolitic-based curriers with the doxorubicin delivery system have also been tested *in vitro* and *in vivo* showing grate potential for applications in anticancer treatment [38]. In addition to synthetic drugs, the ability of zeolite to interact with natural preparations was tested. We will mention an example of caffeine. *In vitro*, clinptilolite has shown satisfactory caffeine encapsulation properties, and the authors suggest that the interaction between zeolite and caffeine involves Van der Wals interactions, H-bonds, and chemical interactions between functional groups and silanol groups of zeolites [39]. Similarly, various zeolite materials were used to design pure and hybrid synthetic scaffolds with olive oil. Cancer cells grew in such newly established solid formulations, showing a slowdown in cell proliferation with respect to time and dose dependence [40].

7. Direct Effect on Tumors

Zeolite clinoptilolite cannot be considered a direct antitumor agent but an adjuvant agent in the treatment of cancer patients. Admittedly, in some published experiments, clinoptilolite showed an antitumor effect *in vitro* and / or *in vivo*. It should be noted that the *in vivo* and *in vitro* effects cannot be compared because of the different mechanisms of action and the fact that zeolites exert their effects *via* the gut. The effect of clinoptilolite in the cell medium on cell viability and on the activity of some key proteins that regulate cell survival, division, and stress response has been demonstrated. Apoptosis has been observed in cells exposed to clinoptilolite as a consequence of changes induced by zeolites, especially in the cellular microenvironment through mechanisms dependent on adsorptive and ion-exchange characteristics [41]. Moreover, *in vitro* cell culture studies show that clinoptilolite inhibits the growth of several cell cultures through inhibition of protein kinase B (c-Akt), induction of $p21^{WAF1 / CIP1}$ and $p27^{KIP1}$ suppressor proteins, and induction of apoptosis [2]. Furthermore, the effect of clinoptilolite on benign and malignant tumors has been demonstrated in rodents and some larger animals, mainly dogs with spontaneous tumors. Interestingly, these dogs have seen a prolongation of life and improvement in general health and sometimes a reduction in tumor size. The most notable results were in the normalization of the levels of aspartate amyotransferase, alanine aminotransferase and alkaline leukocyte phosphatase.

Recent studies have shown the beneficial effect of clinoptilolite on metastasis growth in a mouse model in combination with Lyp-1 - peptide [42]. One of the possible mechanisms of metastasis suppression by Lyp-1 peptide may involve tumor lymphatic spread of tumor. Clinoptilolite can substantially alter the metabolic rates of cancer cells and the increase in the rate of 4-hydroxynonenal (HNE) lipid peroxidation products - removal through increased albumin binding. The combination of clinoptilolite and doxorubicin has also been shown to reduce pulmonary metastases. This is a relevant finding that doxorubicin administration did not affect the level of lipid peroxidation in tumor cells [28]. This interference of clinoptilolites with lipid peroxidation may be responsible for some of the beneficial effects of zeolites in combination cancer therapy. In addition, zeolites can be useful in reducing or eliminating the harmful effects of radio and chemotherapy. Eg. zeolites have been shown to bind histamine [43] and this may be used in the future to eliminate neurogeic inflammatory processes and

neuropathic pain [44, 45]. Unfortunately, we do not yet have systematic clinical studies on the effects of zeolites on the post-therapeutic course of cancer patients. There are, however, many anecdotal descriptions of a significant improvement in the adverse effects of patients treated with anticancer drugs. Therefore, the data reported in the scientific literature undoubtedly indicate the potential beneficial effect of zeolites on the course of the disease following aggressive therapy. Due to their specific physicochemical properties, zeolites could be very useful in the rehabilitation of patients treated for malignant tumors.

8. Conclusion

We can conclude that many cancer patients undergoing cheotherapy and radiotherapy may suffer adverse post-therapeutic effects. Clinoptilolite registered as a medical device (e.g. PMA-zeolite), thanks to its remarkable physicochemical properties, appropriate homogenity and quality, can help reduce or prevent and even eliminate these problems. Therefore, the idea is to use clinoptilolite after aggressive therapy in a more successful and painless treatment of patients with various malignancies, even metastatic cancer.

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