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NEW FINDINGS REGARDING THE BIOMEDICAL IMPACT AND THE ANTITUMOR POTENTIAL OF ZEOLITES (REVIEW)

ACTUALITAȚI PRIVIND IMPACTUL BIOMEDICAL ȘI POTENȚIALUL ANTITUMORAL AL ZEOLITULUI (REVIEW)

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ABSTRACT

Natural zeolites have numerous biomedical applications, mainly because of their proprieties namely ion exchange, adsorption, and catalytic action. In this review we offer a short revision of an ensemble of established articles regarding the use of natural zeolites and some synthetic analogues in the control of oxidative stress and detoxification of organisms, as well as adjunction to prophylactic and therapeutic protocols of some diseases common to both humans and animals, especially cancer and radioprotection. Details such as actual data regarding dosage and way of administration are approached, as well as the advantages and disadvantages of the current techniques used in the preparation and formulation of these compounds.

Keywords: zeolites, prevention, therapy, pathologies, cancer

REZUMAT

Zeoliții naturali prezintă numeroase aplicații biomedicale, bazate în principal pe proprietățile acestora de schimb ionic, adsorbție și cataliză, dintre care unele au deja o largă uzuale clinică. Prin acest review oferim o scurtă revizuire a unui ansamblu de lucrări consacrate în privința utilizării zeoliților naturali și a unor forme modificate ale acestora în controlul stresului oxidativ și detoxificării organismului, respectiv în completarea unor protocoale profilactico-terapeutice ale unor maladii la om și animale, cu trimitere specială la boala canceroasă și radioprotecție. Sunt discutate unele detalii actuale privind dozarea și administrarea zeoliților de interes medical, în corelație cu avantajele și eventualele dezavantaje ale tehnicilor utilizate în prepararea și formularea acestora.

Cuvinte cheie: zeoliți, prevenire, terapie, patologii, cancer

THE BIOCHEMICAL ACTION OF ZEOLITES

Natural zeolites are the ones with the biological effects and thus are of medical interest. Unlike natural zeolites, synthetic zeolites do not have medical properties and they are predominantly used in industry (4, 10). Most biomedical actions of this volcanic compound are provided by their ion exchange, adsorption, and catalytic action proprieties. The biological actions of natural zeolites are based on numerous principles, most of them were verified in human and veterinary medicine, and others are still representing a challenge for researchers in the field (12, 18). The first figure shows the ensemble of these principles in correlation with the diversity of diseases in which the prophylactic and the therapeutic potential of zeolites has already been proven. According to the studied data, there are numerous researches in the field that reveal the prophylactic and therapeutic use of zeolites in various pathologies both in humans and animals alike, the most common way of administration being in powder form and recently, in combination with other remedies as supplements (7, 9, 21).

THE ANTIOXIDANT POTENTIAL

It is well known that the results of metabolic processes are cellular energy and free radicals that can later transform into reactive radicals (reactive oxygen species) that are very harmful to the organism's structures (22). The formation of free radicals is favoured by some nutritional compounds, xenobiotic or medical, and the UV light, alcohol, and tobacco intensify the production of reactive radicals (28). In this context data regarding the extremely injurious effects of oxidative stress should be analysed because it can contribute to the triggering of numerous metabolic and inflammatory diseases (diabetes, atherosclerosis, cata-

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ract, rheumatism, Alzheimer's disease, and other neurodegenerative pathologies) (22). Zeolites interfere in this mechanism through their big surface of contact and the ability to a perform cationic exchange, thus causing the drop of the concentration of free radicals, contributing to the prevention and decrease of oxidative stress. The antioxidant effect of micronized zeolites is based on the use of metallic ions from their structure as cofactors for the activation of antioxidant enzymes (22). In this regard, the most important data were obtained through animal models, such as the one that Saribeyoglu et al. (2011) used rats with oxidative stress-induced hepatectomy (33). The antioxidant effect of zeolites given by the sequestration of free radicals has been proven to be efficient in the prevention and therapy of cancer, immunological imbalances, rheumatism, and other important diseases for humans and animals (5, 11, 16, 17, 26).

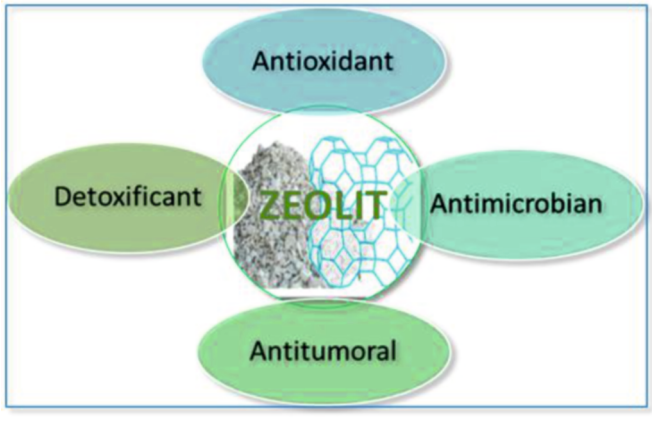

Fig. 1. The main properties of zeolites that the biomedical application are based on

THE DETOXIFICATION, ANTACID AND NEUTRALISING ACTIONS

Due to the lack of toxicity, the low rate of digestive absorption, and the long duration of action, zeolites are excellent digestive and general detoxifiers. This action is rounded by the important antacid and alkalising effects that confer a good neutralisation of gastric content, especially in the case of clinoptilolite. The zeolites also take part in the rebalance of concentration changes of the gastrointestinal tract, determining the functional regulation of pepsin and other enzymes. Another big interest is attributed to research that centres around the catalytic action of zeolites, through which these compounds embed and release enzymes and ions. Because of the large surface that zeolites make available, they can be exploited for their capacity of charging large quantities of enzymes, acting through physical and chemical interactions (22). Regarding the detoxifying action of zeolites, it is believed that these compounds can imbed most toxins, heavy metals, and other injurious substances that frequently have contact with the human and animal organisms (e.g., mycotoxins, dioxins, aromatic amines, acrylamides, polycyclic aromatic hydrocarbon, and aliphatic polyamines). Many studies have been conducted in the past decades in this field, among which abound those that implement adsorbent devices with zeolites for water and food decontamination (22). Zeolites are also researched for their use in the prevention and treatment of gastrointestinal disorders for humans and animals (22). In this context, it is important to mention several studies that proved the reduction of lactate levels during stress assessments due to the use of zeolites (15, 16). The detoxifying effects of zeolites were thoroughly investigated and implemented in veterinary medicine and animal husbandry. Definite results have been obtained regarding the improvement of the health status of farm animals correlated with the removal of injurious substances from the organisms, such as ammonia, nitrites, mycotoxins, and other toxins (Burmanczuk et al., 2015; Kraljević et al., 2018). According to some recent studies, the detoxifying action of zeolites is very efficient in embedding and removing toxic metabolites resulted from long-term chemotherapy, cytostatic and antidiabetic therapies (6, 16). Even though numerous arguments support the benefits of the antioxidant actions of zeolites, there still is a demand regarding thorough studies that evaluate all the advantages of zeolite use for humans and animals alike.

THE ANTIMICROBIAL POTENTIAL

The antimicrobial activity of natural zeolites has been proven experimentally and clinically (9, 13, 14, 25, 26). The most relevant results were obtained by Al-Nasser et al. (2011), these being that through zeolite supplementation (1,0-2,0 %) of the chicken feed significantly reduces the *Salmonella* incidence on the body and the carcases of chicken. This study also illustrates the positive effects of zeolites on the productive performances of the chicken (3). In the last decades, the use of zeolites has extended to microbial pollution control, with good results being achieved on Gram-positive bacteria, Gram-negative bacteria, *C. albicans*. *P. aeruginosa*, *St. aureus,* and *E. coli* (5, 7, 10). Other biological effects with possible medical application of zeolites. The propriety of zeolites to imbed and remove ammonia opens new perspectives in the diversification of the dialysis procedures that can now rely on simpler and portable systems. The adsorbent action of zeolites could be applied even in procedures of inhalational anaesthetic through devices that can adsorb the gas that the patient inhaled in order to remove it as fast as possible to prevent the harmful effects on the organism. The external application of

zeolites has been another preoccupation of scientists and medical practitioners, which have proven to be useful in dermatology and cosmetology. In this regard, we find that the most relevant effects of zeolites are photoprotection against UV lights as well as the beneficial action on wounds and surgical incisions, which is manifested through the reduction of the healing time (27). Some zeolites can also influence the activity of bone structures, stimulating their growth, or by fostering the in vivo production of some growth factors (TGFβ) in adult cell lines similar to osteoblasts (22). Zeolites can influence the evolution of diabetes as well, some studies conducted on rats with alloxan-induced diabetes revealed the capacity of natural clinoptilolite to prevent the development of specific complications of this disease (20). It is important to note the beneficial effects of natural zeolites in the control of neurodegenerative diseases, especially in Alzheimer's disease which is the most widespread form of dementia, and it currently affects millions of people (30). In this disease the gut microbiota changes due to an unhealthy lifestyle, thus affecting the intestinal permeability, which is also involved in the progressive character of this disease and also other neurological disorders (8, 34). In this regard, the zeolite-based products could represent a good alternative in controlling Alzheimer's disease, based on their well-known detoxifying, antioxidants, and anti-inflammatory properties. Recent studies show promising potential of zeolite-based products in neurodegenerative disorders, though they are not yet convincing enough to further any other clinical research in the treatment of Alzheimer's disease, which continues to be a disorder of medical and social interest. It has also been noted the possibility of using zeolites as medical biosensors, in the form of simple and cheap measuring systems, that can have high sensibility and specificity. Zeolites have immunological and immunizing applications as well, mainly based on the adjuvant stimulatory of silicates effect. Out of many studies that have followed this action, some succeed in proving the in vivo potential of zeolites to polyclonal activate T human cells (2, 20).

THE ANTITUMOR POTENTIAL OF ZEOLITES

Of great interest are the concerns regarding integrating zeolites in prophylactic and treatment protocols of cancer for humans and animals, because of the abundance of research and clinical applications in this field (35, 36). Out of all the obtained results from the association of zeolites in the therapy of cancer, the most relevant are those reported by Sağir et al. (2016) in some clinical forms of cancer in dogs, as well as experimentally induced cancer in rats. Sağir et al. (2016) reported an improvement in the health status, an extension in the life expectancy, and lower mortality rates for animals that were treated with natural clinoptilolite (31). In this context it is worth mentioning other studies that proved natural clinoptilolite to have a strong immunostimulating effect, probably constituting an antimetastatic way of action (28, 29). In the oncological therapy field, large studies were conducted on the preparation and utilisation of zeolites as reservoirs with a prolonged release for anticancer medication. In this regard, the study of Abd-Elsatar et al. (2019) is important because it is based on using three zeolites (ZSM-5, zeolite A, and faujasite zeolites-NaX) that are prepared to act as systems of prolonged release of 5-fluorouracil (5-Fu) as a treatment for colon cancer. Their results revealed a distinct antitumor action of these zeolites that carried 5-Fu against cancerous colon cells (CaCo-2) (1). Given the impact that zeolites have on the prevention and treatment of cancer, it is important to consider that further studies should be conducted to establish the zeolite applications in oncology.

Particularities regarding the mechanism of action of zeolites in cancer

It is considered that one of the mechanisms of action of zeolites in the prevention and treatment of some forms of oncological or haematological diseases would consist of the limitation of chromosomal deviation, thus participating in normalising genetic information (18). Another accepted theory suggests that zeolites have a direct action over cancerous cells determining their death through a similar mechanism with apoptosis. These actions are also potentiated by the strong ability to adsorb and eliminate toxic substances and also the immunomodulation of the volcanic tuff. Biologically speaking the organism possesses all the defence mechanisms that also participate in cancer, especially when zeolites are supplemented. As it is well known some tumours (renal carcinoma, neuroblastoma, choriocarcinoma, and even malign melanoma) can spontaneously regress until it completely remission. Such self-healing is only possible when the organism benefits from optimal conditions to fully express all functional activities. Regarding the efficiency of the general mechanism which lies at the basis of the therapeutical way of action of zeolites, it seems that this is less due to its chemical composition and more related to its spatial configuration (20, 36). It is known that zeolites are mainly administered orally and they benefit from reduced digestive absorption. As a result, a very small quantity of zeolite gets to circulate in the bloodstream and distribute throughout the organism, but this being enough to imbed and eliminate most toxins accumulated over time. In this regard, most of the ingested zeolite transits the gastrointestinal tract and retains toxins that circulate via the

bloodstream, and they finally eliminate through the stool and in fewer forms through the renal and cutaneous systems. This explains the mild alterations of the colour and smell of the urine, and also the hyperhidrosis secondary to zeolite treatment. Another form of administration of zeolites in cancer therapy is the cutaneous way. In this regard, it is worth mentioning that almost two decades ago Pavelic and Hadzija (2003) apply locally a fine powder of clinoptilolite in a study conducted on dogs with different types of skin cancer and they observe a significant reduction of the proliferation and multiplication of cancerous cells.

These clinical studies were later correlated to in vitro conducted research that demonstrated the fact that clinoptilolite processed into a fine powder inhibits protein kinase B (c-Akt) and induces the expression of a tumour-suppressing protein (p21 WAF1/CIP1 and p37 KIP1), thus stopping the tumour growth in many cell lines (27). Synthesising the results of many studies conducted in the field it is becoming clear that in the treatment of cancer patients the administration of zeolites-based products twice a day, can reduce the toxins accumulated in this pathology. The beneficial effects of zeolites are seen the same over an organism that is being treated with radiotherapy or with cytostatic medication, when they act as an excellent adjuvant involved in the elimination of the cellular residues from the destroyed cancerous cells, thus contributing to the maintenance of the general health and vitality of patients (19).

The use of zeolites in radiotherapy subjected patients

Great interest is also attributed to utilising zeolites as radioprotection in radiotherapy subjected patients. Initially, there was confusion that regarded zeolites as decreasing the patients' response to radiotherapy. The hypothesis that states the fact that the direct action of the radioactive isotope beam (cobalt, caesium, and radium) destroys the cancerous cells is outdated. Zeolites also contribute to the elimination of these isotopes from the organism. Returning to the general explanation of the irradiation phenomenon, which also includes targeting cancerous cells, it is to be noted the fact that this action is not due to the result of the direct contact with the radioactive isotopes, but it is the effect of an irradiation fascicle formed by the disintegration of the isotopes. According to this principle, radiotherapy devices can controllably disintegrate and conduct the irradiation fascicle over the tumour area. Thus, the isotopes do not leave the irradiation device and the generated fascicle is either electromagnetic or corpuscular (with electrons, protons, and other nuclear particles). Based on this data it can be concluded the fact that radioactive atoms or isotopes do not reach the patient's body. Regarding the action of zeolites, it is clear that they do not interact with the irradiation agent, but they provide radioprotection that benefits patients over the injurious action of the irradiation process.

On the other hand, the administration of the volcanic tuff assures the elimination of the oncogenic residues resulted from the destruction of the cancerous cells due to radiotherapy. Zeolites can have a direct action through the adsorption of tumour residues, and also indirectly through the stimulation of the immune system with the enhancement of the phagocytosis process. Thus, after the elimination of the cancerous residues, the risk of injury and transformation into cancerous entities of other healthy cells decreases significantly. In conclusion, zeolites help to maintain untainted genetic information in healthy cells, even if they are exposed to strong mutagen factors like irradiation. There are some exceptions to these principles. Among them, metabolic radiotherapy is the most well-known and it implies the administration of radioactive isotopes that have an affinity to some tissues. In this kind of radiotherapy that is rarely used (such as the practice of administering Sr^{89} to treat prostate cancer), zeolite administration is not recommended.

The utilisation of zeolites in patients subjected to cytostatic therapy

The mechanisms that have previously been analysed sit at the basis of the association of zeolites in the oncological cytostatic therapeutic protocols. There are some particularities regarding the mechanism of action of chemotherapeutic agents that reach the cancerous cells via the bloodstream. These chemotherapeutic agents have a very short duration of action that corresponds to the maintaining of the maximum plasmatic concentration and it lasts only for a few hours after administration. Thus, the efficiency of the antitumor action of cytostatic drugs reduces together with the drop in the plasmatic concentration, in return, the side effects are long-term (10, 11). Some cytostatic agents, such as cisplatin, could be still found in tissues many months after administration (10, 20). Regarding the action of zeolites, they are believed to cleanse the blood of chemotactic toxins because the lower the plasmatic concentration of these residues. From the logical analysis of this data has shown that zeolites may lower the efficacy of cytostatic agents if it is present in the gastrointestinal tract during the time that cytostatic agents reach their maximum plasmatic concentrations. According to these principles, it would be advisable not to administer zeolites at the same time with cytostatic agents. It is recommended to leave three hours break before and twelve hours after the administration of cytostatic drugs. The use of zeolites outside these periods is imperative to eliminate the accumulated toxins that have already lost their an-

titumor effect but continue to weaken the organism that already suffers from the cancerous pathology. Based on the presented data, it can be stated the fact that the volcanic tuff can efficiently contribute to the elimination of the residues that resulted from the cellular disintegration.

Other applications of zeolites in oncology

It is well known that patients that suffer from oncological pathologies will eventually develop anorexia that inevitably leads to cachexy. The evolution of these syndromes can be diminished or even stopped by the beneficial action of zeolites. For this purpose, it is advised to supplement the diet with powdered zeolites (1%). Even though the mechanisms of actions of zeolites in these syndromes are not fully understood, it is presumed that such effects are due to its detoxifying and enzymatic catalysis proprieties. On the other hand, the preventive action of zeolites in cases of possible gastrointestinal dysfunctions and microbial infections that could develop during conventional oncological treatments should not be overlooked. Zeolites also have an antacid without affecting the action of gastric enzymes, so it is an efficient treatment in gastritis, gastroesophageal reflux disease, and ulcers. Zeolites adsorb and eliminate both pathogens and toxins alike. It should be noted that zeolites also help the kidney through the cleansing of the blood and also through the neutralisation of the circulated ammonia. Zeolites act as a filter in the digestive system and significantly reduce the number of patients that require dialysis. Based on the good results obtained from administering zeolites in combination with other natural remedies (propolis, royal jelly, Common couch tea) to treat osteoporosis or osteomalacia secondary to gastric cancer (20).

Zeolites administration for cancer patients

According to some clinical observations, to potentate zeolites used as an adjuvant in oncological treatments, it should be used for a long period. The zeolite therapy should start after the diagnosis and continue through the oncological treatment and even after. To establish the administration protocol of zeolites the general health status of the patient and the type of oncological treatment should be taken into consideration. It is generally advised to administer one or two teaspoons of zeolites twice or three times a day on an empty stomach (28).

There are many forms of presentations of zeolites on the market today, but the micronized zeolite powder is preferred to capsule and tablets that also contain different excipients. Generally, the addition of excipients is not justified in nutraceuticals that have only one active substance and are not perishable (12, 19).

The use of zeolites in radioprotection

Currently, it is unanimously accepted that the volcanic tuff is an excellent protective agent for people that work in a high risk of radioactivity environment (radiology, radiotherapy, chemical industry, mining, agriculture). There is sufficient data that proved the natural zeolites' ability to imbed some radioactive isotopes (^{90}Sr, ^{137}Cs, ^{60}Co, 45Ca, ^{51}Cr) (23, 24). Zeolites are often used because of their efficacy in radioprotection. A good example is the case of the Chernobyl nuclear accident (1986) in which impressive quantities of clinoptilolite (500.000 tonnes) have been used. A part of this quantity was used to construct the shell of the reactor, causing a drastic drop in radioactivity, and the other part was used to decontaminate water, thus reducing pollution with ^{131}Cs and ^{90}Sr. The diet of both locals and animals was also supplemented with clinoptilolite to reduce the harmful effects of Cs (27). Zeolites were also used to protect the radiology personnel, proving to be quite effective. In this regard the recommended protocol is based on the administration of a teaspoon of powdered zeolites once or twice a day, five days a week; the dose can vary depending on the weight and the severity of exposure (28).

DATA REGARDING THE EVALUATION OF ZEOLITE TOXICITY AND OTHER SIDE EFFECTS

Out of the numerous researchers that are preoccupied with the evaluation of zeolite toxicity, particular results were reported by the research team led by Scott (2003) that managed to prove activated clinoptilolite's lack of toxicity. The conclusion resulted after experimental administration of a big dosage orally in rats (2-200 mg and 2-500 mg respectively 20-5000 mg/animal a day, for 6-14-30 days) (32). The same researchers continue the study by administering powdered clinoptilolite 25% in rats feed during the gestation and lactation periods. During this study, it has been noted a rise in the nests that were preparing for birth and a reduction of the bodyweight of the animals, without any teratogen effects. All of this completely justifies the absence of clinoptilolite toxicity and other harmful effcets of clinoptilolite on the reproductive process in general. There is however a disadvantage regarding the dosage of natural zeolites used for medical purposes because of the size of the particles. There is a ratio between the dimension of the particles and the activation degree of the zeolite,which indicates the fact that together with the rise of the number of particles there is an increase in the external surface of the powdered mass, which activate the zeolite without polluting it. The tribomechanical micronisation of Clinoptilolite with a dimension of approxi-

matively 3 m²/g is tribomechanically micronised when it reaches 1000 m²/g. This technique is used to obtain the product Zeolit Activat Clinoptilolit (ZCA), biologically tested and registered by an Austrian company that used it as a medical device to formulate many zeolite-based products known all over Europe (DM-TUV CE 0197 from 2006).

CONCLUSIONS

The findings of this review are that the biomedical research of zeolites does not have the aim to discover a new remedy but to develop a nutraceutical for humans and animals that can help improve living conditions and to efficiently be combined with other drugs.

Out of the many biomedical applications of natural zeolites, a major impact is attributed to the detoxifying potential of this vehicle that is also involved in the elimination of toxic and drug residues resulted from various therapies. Although there are sufficient encouraging results, there is still a need to continue the research to investigate the biomedical potential of zeolites and the many benefits that they can bring to the health of humans and animals.

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