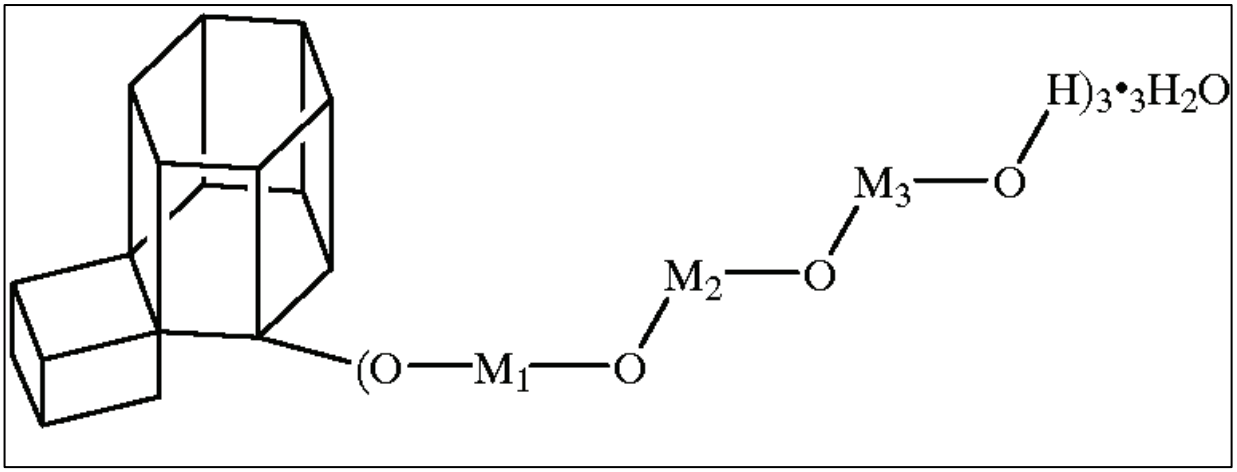
Natural Cellular Defense



(where M_1 is silicon, M_2 is magnesium, M_3 is aluminum)

4,5 di-cyclo, disilico, dimagnesium, dialumino, oxyo, trihydrate

SCIENTIFIC RESEARCH MONOGRAPH

by Rik J. Deitsch

ABOUT THE AUTHOR

Rik J Deitsch

Rik J Deitsch is the Chief Executive Officer of Nutra Pharma Corporation - a publicly traded Biotechnology holding company and incubator dedicated to researching neurological disorders and viral diseases. Mr. Deitsch served as the President of NDA Consulting Inc., a biotechnology research group that provided consulting services to the pharmaceutical industry. Rik J. Deitsch also serves as the Chairman of the Waiora Scientific Advisory Board. In this role, he is responsible for overseeing the direction and development of Waiora's products as they relate to the company's overall product strategy. Leading a team of knowledgeable, well-respected and highly credentialed physicians and healthcare professionals, the Board recommends formulations and ingredients to create efficacious products for Waiora.

Research conducted by Rik J Deitsch provided some of the beginning fundamentals for the development of some powerful new drugs. Mr. Deitsch has several papers and posters on rational drug design using computer simulations. He teaches several courses for Florida Atlantic University's Continuing Education Department and College of Business. Mr. Deitsch also teaches physician CME courses internationally, lecturing on lifestyle choices in the prevention and treatment of chronic disease states. He is also the co-author of *Are You Age-Wise*, a book that reviews current research in healthy aging as it relates to lifestyle choices and supplementation (*www.areyouagewise.com*).

About this Publication

The information presented in this monograph is intended for professional education and is obtained from published research, articles, and books. This monograph is not intended to replace the care of a licensed health professional in the diagnosis and treatment of illness.

Key Points

Natural Cellular Defense is derived from a naturally-occurring mineral zeolite. Zeolites are considered 100 percent safe and non-toxic by the FDA.

Natural Cellular Defense and its constituent zeolite have been shown to have the following functions:

- Retains the natural zeolite property of reducing cancer risk
- Acts as a potent anti-oxidant
- May aid in balancing bodily pH levels
- Acts to chelate and remove heavy metals from the system
- Reduces the incidence of diarrhea
- Improves nutrient absorption in the digestive tract
- Acts to balance digestive pH, thus reducing acid reflux
- Acts to stabilize immune system function (immunomodulatory)
- Acts as a broad spectrum anti-viral agent

1. Introduction

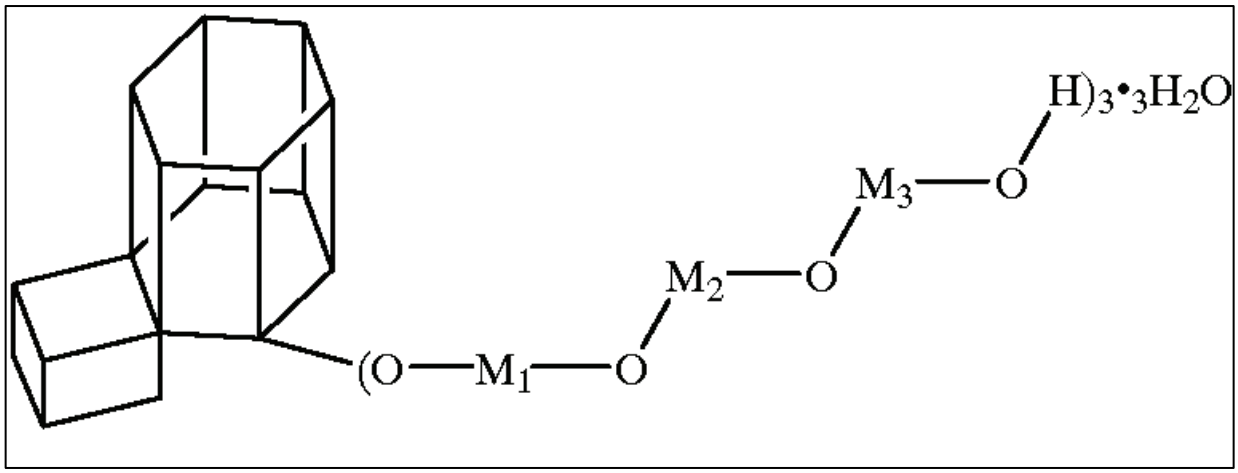
Zeolites are hydrated natural and synthetic microporous crystals with well-defined structures containing AlO_4 and SiO_4 tetrahedra linked through the common oxygen atoms. Most common natural zeolites are formed by alteration of glass-rich volcanic rocks (tuff) with fresh water in playa lakes or by seawater. The structures of zeolites consist of three-dimensional frameworks of SiO_4 and AlO_4 tetrahedra. The aluminum ion is small enough to occupy the position in the center of the tetrahedron of four oxygen atoms, and the isomorphous replacement of Si^{4+} by Al^{3+} produces a negative charge in the lattice. The net negative charge is balanced by the exchangeable cation (sodium, potassium, or calcium). Zeolites have been extensively used in various industrial applications based on their properties to act as catalysts, ion exchangers, adsorbents, and detergent builders. It is also known that silicates and aluminosilicates possess biological activity, either positive or negative. Talc and silica have been used in skin care for many decades, while well defined structures and catalytic activity make aluminosilicates an attractive model system for protein and enzyme mimetics. Recent results have also demonstrated that natural, biologically nontoxic zeolites are very effective as glucose adsorbents, and this has been suggested as a potential medication for individuals suffering from diabetes mellitus.

Natural zeolites are crystalline, hydrated alluminosilicates of alkali and alkaline earth cations, having three-dimensional structures. They are characterized by the ability to lose and gain water reversibly and to exchange constituent cations (positively-charged particles) without major change of structure. The basis of interest in the biological effects of zeolites concerns one or more of their physical and chemical properties, such as ion exchange capacity, adsorption and related molecular sieve properties.

For the purpose of this Review, only the properties of zeolites that address its effects as a supplement will be investigated. Although the mechanism of action of many of these claims is not well understood, the complex structure of the zeolite in question may provide clues to this mechanism. The zeolite acts as a 'cage' and allows the molecule to trap a variety of ions and compounds. By trapping charged particles, the zeolite can: act as an antioxidant, balance pH levels, lower incidence of heavy metal damage, improve nutrient absorption and reduce gastric reflux. The cage may also trap potential carcinogens, thereby reducing the risk of developing cancer. The anti-viral activity of zeolites may be founded in the molecule's ability to trap viral particles during assembly, thereby preventing viral assembly and proliferation.

This paper will endeavor to categorize the major claims made by Natural Cellular Defense.

2. Description

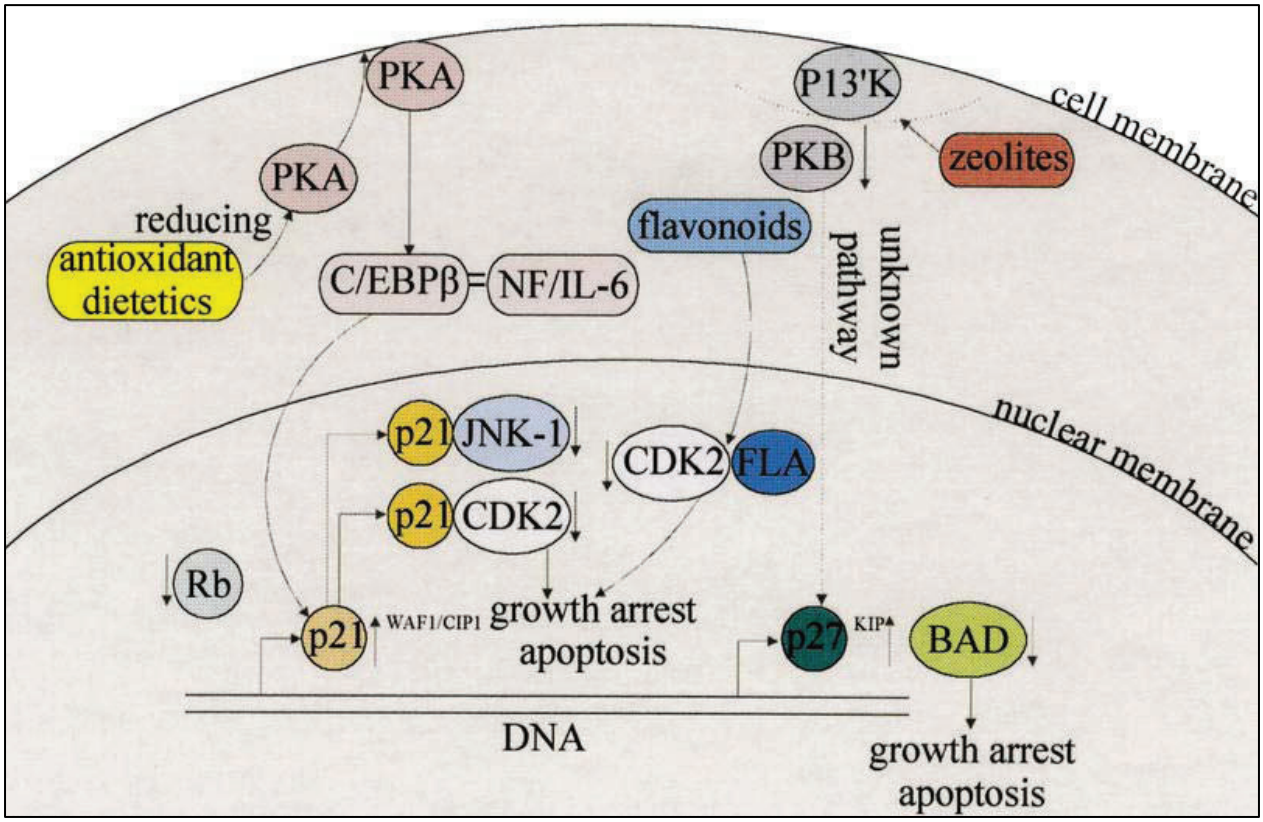


(where M_1 is silicon, M_2 is magnesium, M_3 is aluminum)

4,5 di-cyclo, disilico, dimagnesium, dialumino, oxyo, trihydrate

Natural Cellular Defense is identified generically as 4,5 di-cyclo, disilico, dimagnesium, dialumino, oxyo, trihydrate ($3Mg^{2+}$ $3Al_2$ O_3 $3SiO_2$ $3H_2O$), which is a magnesium aluminosilicate. It is in the acetate, sulfate, chloride, or brominate form. Natural Cellular Defense is a slightly white, odorless, tasteless liquid. The zeolite particles are negatively charged in the entire pH range (pH 1–11). Electron microscopy shows an absence of fibers, and most particles are round with a very rough surface. The absence of fibrous, positively charged particles is encouraging since such particles are present in asbestos and erionite zeolites, which are highly carcinogenic and mutagenic. In addition, activated zeolite particles do not catalyze the production of hydroxyl radicals, unlike asbestos or erionite. It seems that absence of fibrous particles capable of producing hydroxyl radicals makes this zeolite sample nontoxic and noncarcinogenic, at least when applied orally.

3. Reducing Cancer Risk Factors



Mechanisms of action of potential anti-cancer supplements

The development of modern industry has caused increasingly serious pollution in the environment constituting a catastrophic health risk - including cancer. Cancer prevention is thus one of the challenges facing scientists in the 21st century and removal of carcinogens from the environment is an important step. Nitrosamines are probably the most widespread carcinogens, existing in the workplace, processed meats, cigarette smoke and beer. They are even produced in the stomach by the reaction of secondary amines and nitrite (NO_2^-) both taken from foods. A 1976 report of German scientists showed that the uptake of nitrosamines for a person was as much as 700ng daily. The occurrence of gastric cancer was related to the nitrosamines in the stomach. Many carcinogenic agents like nitrosamines or their precursors enter the human stomach through diet and drinking. No matter how carefully food is prepared; there is a level of nitrosamine content. Environmental pollution makes this hidden trouble more serious, because of the contaminated food and polluted atmosphere. However, although nitrosamines are well-known carcinogenic substances, they require metabolic activation before reaction with DNA to cause mutation and cancer. Therefore, it is

possible and necessary to trap the nitrosamines in the digestive tract provided a selective adsorbent material is employed. To seek this functional material, zeolites are considered as the best candidates. Zeolites and molecular sieves have been employed in slow release drugs, enzyme mimetic drugs, anti-tumor drugs and additives in cigarettes to remove carcinogenic agents like nitrosamines.

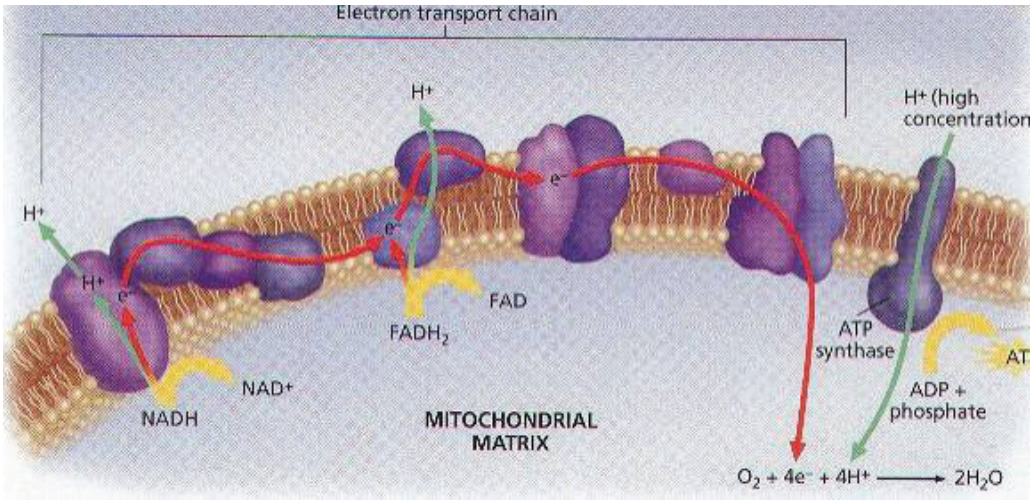
Numerous natural compounds are commonly used for the treatment of various diseases, including green tea and soybean extracts. Recent findings indicate that dietetic products and antioxidant compounds also have a beneficial effect particularly in cancer patients. In many cases the exact mechanism of their action is not fully understood. In the published literature the effect of natural zeolite particles on development of several cancer models in-vivo and in-vitro was studied. It has been found that zeolites may act as anticancer therapeutic agents in in-vivo animal studies and in tissue culture cell models. The constituent natural zeolite from Natural Cellular Defense applied orally in mice and dogs suffering from a variety of tumor types led to a significant shrinkage of some tumors and improvement in overall health status in some animals. The range of effects was diverse, ranging from negative antitumor response, to normalization of biochemical parameters, prolongation of life span, and decrease in tumor size. The best results in animal models were observed in the treatment of skin cancer in dogs, suggesting that adsorption of some active components is responsible for zeolite activity (direct contact action). Complementary studies performed in tissue culture indicated that zeolite treatment affects proliferation and survival of several cancer cell lines. Addition of zeolite inhibited cell proliferation in a concentration-dependent manner, in part due to induction of inhibitors of cycline dependent kinases and induction of programmed cell death. The data indicates that zeolite treatment might affect cancer growth by attenuating survival signals and inducing tumor suppressor genes in treated cells. In addition, toxicology studies on mice and rats demonstrated that the treatment does not have negative effects.

Finely ground natural zeolite powder has also been shown to induce activation of $p21^{WAF1/CIP1}$. As a universal inhibitor of cyclin-dependent kinases and one of the target genes of the tumor suppresser p53, $p21^{WAF1/CIP1}$ can act as a tumor suppresser through its ability to control cell cycle progression. Activation of $p21^{WAF1/CIP1}$ may halt the growth of tumors by directly suppressing growth signals. However, tissue culture experiments demonstrated that activated zeolite particles inhibit protein kinase B/akt, another kinase involved in antiapoptotic processes and cancer promotion. This happens only when growth of cells in tissue cultures is stimulated by the addition of growth factors. Zeolite particles might adsorb growth factors or prevent interaction of protein kinase B with membranes, where it is phosphorylated by phosphatidylinositol 3-kinase. It has recently been shown that inactivation of protein kinase B by, for example, the novel tumor suppressor molecule PTEN also results in induction of the tumor suppressor-CDK inhibitor $p27^{KIP1}$.

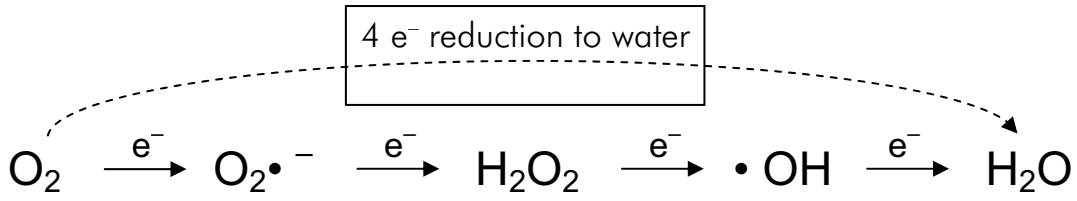
There also seems to be a relationship between $p21^{WAF1/CIP1}$ and another protein kinase involved in cell "decisions" about proliferation, arrest or apoptosis, namely c-Jun N-terminal kinase (JNK) 1. JNK-1 is a member of the recently discovered stress-activated protein kinases. Interestingly, while in reaction to stress such kinase activation results in apoptosis, its activation in some cancer cells actually promotes uncontrolled proliferation. This is particularly obvious in the human lung adenocarcinoma cell line A549. Research has shown that $p21^{WAF1/CIP1}$ inhibits JNK-1, and recent work indicates that those two molecules form a tight complex. Inactivation of JNK-1 may be part of the reason why antioxidants enhance cytotoxicity of chemotherapeutic agents towards cancer cells, while, on the other hand, they protect neurons from apoptosis caused by free radical damage.

4. Potent Antioxidant

Oxygen is actually a toxic byproduct of the metabolism of lower cell organisms, and the body uses it to produce energy. Oxygen free radicals are created through a biochemical process at the cellular level. Oxygen and glucose are used to produce adenosine triphosphate (ATP) through oxidative phosphorylation.

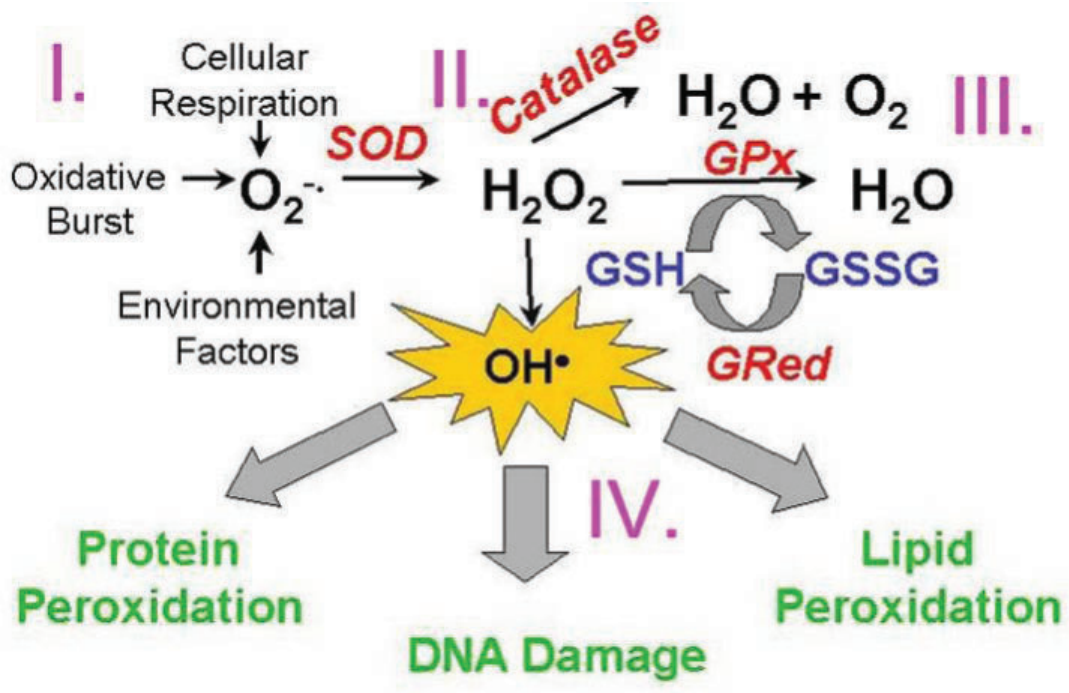


Oxidative phosphorylation is a process during which electrons not bound to an oxygen molecule move from one such molecule to another seeking to bind to other unpaired electrons. These oxygen molecules that contain unpaired electrons are called oxygen free radicals.



One percent to three percent of the oxygen we breathe creates oxygen free radicals, as do natural aging and chronic disease. In small amounts, some oxygen free radicals help to clean cells by taking part in phagocytosis, a function of a normal immune system, but as production of these radicals increases, they begin to attack and destroy cells. As their levels increase, oxygen free radicals attack and oxidize DNA, genetic molecular material that controls cell growth and development. Oxidation of DNA may lead to the adverse effects of aging, such as wrinkled skin, organ dysfunction, and cancer. As oxygen free radicals travel through the

blood, they set the stage for heart, blood vessel, cerebrovascular, and skeletal muscle disease by making it more difficult for cells to repair themselves.



Free radicals can damage the intima in blood vessels, causing inflammation and thereby leading to increased plaque formation, which can contribute to stroke and cardiac disease. Oxygen free radicals also free iron, which is usually tightly bound to protein molecules. Excessive levels of free iron are associated with Alzheimer disease, dementia, and Parkinson disease. In addition, oxygen free radicals cause an increase in neuronal loss by changing DNA structure. When a significant number of neurons are degraded, the central nervous system can no longer maintain homeostasis, and physiologic functions such as receptor-mediated signal transmission necessary to memory may become defective or be lost.

The cage structure of Natural Cellular Defense may help to trap free radicals, thereby inactivating them and preventing further damage to the surrounding tissue. This is completely unlike the action of the classic antioxidants. Compounds that have antioxidant properties include the vitamins A, C and E as well as the mineral selenium. There are also a host of other antioxidant compounds, including: flavanoids, catechins and specific enzymes. All of these antioxidants function by acting either as an electron donor or electron acceptor. This action stabilizes the free radical and halts the free radical cascade which would normally lead to further damage of the system and an eventual catastrophe (heart attack, stroke, cancer, etc..). All of these classic antioxidants have the ability to exist with one extra electron or one less electron without becoming a free radical in turn. Natural Cellular Defense may support

the action of these antioxidants through an entirely different mechanism. By literally trapping highly reactive free radicals, these dangerous compounds are inactivated and are easily eliminated from the system.

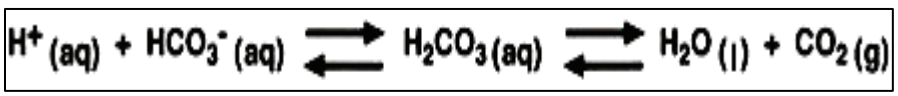
5. Systemic pH levels

The body has a wide array of mechanisms to maintain homeostasis in the blood and extracellular fluid. The most important way that the pH of the blood is kept relatively constant is by buffers dissolved in the blood. Other organs help enhance the homeostatic function of the buffers. The kidneys help remove excess chemicals from the blood. It is the kidneys that ultimately remove (from the body) H^+ ions and other components of the pH buffers that build up in excess. Acidosis that results from failure of the kidneys to perform this excretory function is known as metabolic acidosis. However, excretion by the kidneys is a relatively slow process, and may take too long to prevent acute acidosis resulting from a sudden decrease in pH (*e.g.,* during exercise). The lungs provide a faster way to help control the pH of the blood. The increased-breathing response to exercise helps to counteract the pH-lowering effects of exercise by removing CO_2, a component of the principal pH buffer in the blood. Acidosis that results from failure of the lungs to eliminate CO_2 as fast as it is produced is known as respiratory acidosis.

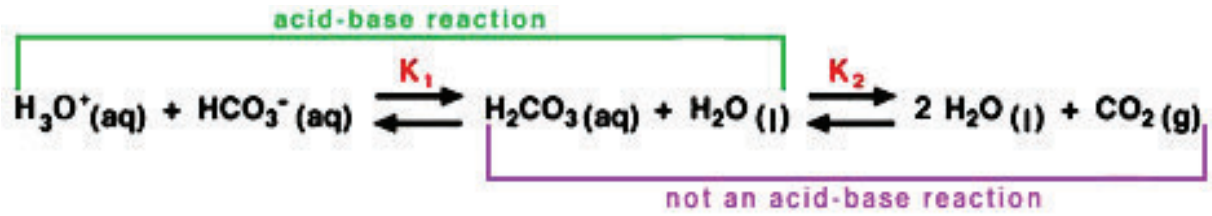
The kidneys and the lungs work together to help maintain a blood pH of 7.4 by affecting the components of the buffers in the blood. Therefore, to understand how these organs help control the pH of the blood, we must first discuss how buffers work in solution.

Acid-base buffers confer resistance to a change in the pH of a solution when hydrogen ions (protons) or hydroxide ions are added or removed. An acid-base buffer typically consists of a weak acid, and its conjugate base (salt). Buffers work because the concentrations of the weak acid and its salt are large compared to the amount of protons or hydroxide ions added or removed. When protons are added to the solution from an external source, some of the base component of the buffer is converted to the weak-acid component (thus using up most of the protons added); when hydroxide ions are added to the solution (or, equivalently, protons are removed from the solution), protons are dissociated from some of the weak-acid molecules of the buffer, converting them to the base of the buffer (and thus replenishing most of the protons removed). However, the change in acid and base concentrations is small relative to the amounts of these species present in solution. Hence, the ratio of acid to base changes only slightly. Thus, the effect on the pH of the solution is small, within certain limitations on the amount of H^+ or OH^- added or removed.

By far the most important buffer for maintaining acid-base balance in the blood is the carbonic-acid-bicarbonate buffer. The simultaneous equilibrium reactions of interest are:



To more clearly show the two equilibrium reactions in the carbonic-acid-bicarbonate buffer, the equation is rewritten to show the direct involvement of water:



The equilibrium on the left is an acid-base reaction. Carbonic acid (H_2CO_3) is the acid and water is the base. The conjugate base for H_2CO_3 is HCO_3^- (bicarbonate ion). Carbonic acid also dissociates rapidly to produce water and carbon dioxide, as shown in the equilibrium on the right. This second process is not an acid-base reaction, but it is important to the blood's buffering capacity. Note that as acid is added, the pH decreases and the buffer shifts toward greater H_2CO_3 and CO_2 concentration. Conversely, as base is added, the pH increases and the buffer shifts toward greater HCO_3^- concentration.

Other buffers perform a more minor role than the carbonic-acid-bicarbonate buffer in regulating the pH of the blood. The phosphate buffer consists of phosphoric acid (H_3PO_4) in equilibrium with dihydrogen phosphate ion ($H_2PO_4^-$) and H^+. The phosphate buffer only plays a minor role in the blood, however, because H_3PO_4 and $H_2PO_4^-$ are found in very low concentration in the blood. Hemoglobin also acts as a pH buffer in the blood. The hemoglobin protein can reversibly bind either H^+ (to the protein) or O_2 (to the Fe of the heme group). When one of these substances is bound, the other is released. During exercise, hemoglobin helps to control the pH of the blood by binding some of the excess protons that are generated in the muscles. At the same time, molecular oxygen is released for use by the muscles.

Being amphoteric, zeolites are partly soluble in acid or alkaline media, but within the physiological pH range the solubility is generally low. Minimal amounts of free aluminium or silicium from the ingested zeolites are resorbed from the gut. In view of the ion exchange properties, zeolites may be expected to change the ionic content, pH and buffering capacity of their surroundings. The zeolite cage system may exchange for varying excess ions found in the zeolite's immediate environment. This would have the overall effect of buffering the surrounding system and regulating pH to near-physiological levels.

6. Heavy Metals and Chelation

Many toxic heavy metals have been discharged into the environment as industrial wastes, causing serious soil and water pollution. Lead (Pb^{+2}), Copper (Cu^{+2}), Iron (Fe^{+3}) and Chromium (Cr^{+3}) are especially common metals that tend to accumulate in organisms, causing numerous diseases and disorders. They are also common groundwater contaminants at industrial and military installations. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic. These metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the WHO. Heavy metals have been used by humans for thousands of years. Although several adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues, and is even increasing in some parts of the world, in particular in less developed countries, though emissions have declined in most developed countries over the last 100 years. Cadmium compounds are currently mainly used in re-chargeable nickel-cadmium batteries. Cadmium emissions have increased dramatically during the 20th century, one reason being that cadmium-containing products are rarely re-cycled, but often dumped together with household waste. Cigarette smoking is a major source of cadmium exposure. In non-smokers, food is the most important source of cadmium exposure. Recent data indicate that adverse health effects of cadmium exposure may occur at lower exposure levels than previously anticipated, primarily in the form of kidney damage but possibly also bone effects and fractures. Measures should be taken to reduce cadmium exposure in the general population in order to minimize the risk of adverse health effects. The general population is exposed to lead from air and food in roughly equal proportions. During the last century, lead emissions to ambient air have caused considerable pollution, mainly due to lead emissions from petroleum. Children are particularly susceptible to lead exposure due to high gastrointestinal uptake and the permeable blood-brain barrier. Blood levels in children should be reduced below the levels so far considered acceptable, recent data indicating that there may be neurotoxic effects of lead at lower levels of exposure than previously anticipated. Although lead in petroleum has dramatically decreased over the last decades, thereby reducing environmental exposure, phasing out any remaining uses of lead additives in motor fuels should be encouraged. The use of lead-based paints should be abandoned, and lead should not be used in food containers. In particular, the public should be aware of glazed food containers, which may leach lead into food. Numerous processes exist for removing dissolved heavy metals, including ion exchange, precipitation, phytoextraction, ultrafiltration, reverse osmosis, and electrodialysis. The use of alternative low-cost materials as potential sorbents for the removal of heavy metals has been emphasized recently.

The structures of zeolites consist of three-dimensional frameworks of SiO_4 and AlO_4 tetrahedra. The aluminum ion is small enough to occupy the position in the center of the tetrahedron of four oxygen atoms, and the isomorphous replacement of Si^{4+} by Al^{3+} produces a negative charge in the lattice. The net negative charge is balanced by the exchangeable cation (sodium, potassium, or calcium). These cations are exchangeable with certain cations in solutions such as lead, cadmium, zinc, and manganese. The fact that zeolite exchangeable

ions are relatively innocuous (sodium, calcium, and potassium ions) makes them particularly suitable for removing undesirable heavy metal ions from the environment and bodily systems. One of the earliest applications of a natural zeolite was in removal and purification of cesium and strontium radioisotopes.

Studies have shown that the constituent zeolite in Natural Cellular Defense has a high affinity for trapping lead, cadmium and other potentially harmful heavy metals. Through the process of cation exchange, Natural Cellular Defense may lower overall heavy metal exposure in individuals. This would have a dramatic effect in the risk reduction of certain cancers and heart disease – the two leading causes of death in the United States.

7. Digestive disorders

Natural silicate materials have been shown to exhibit diverse biological activities and have been used successfully as a vaccine adjuvant and for the treatment of diarrhea.

The potential growth promoting action of natural zeolites has been attributed to their high affinity for ammonium ions, resulting to the reduction in the uptake of ammonia produced from deamination of proteins during the digestive processes via the intestinal wall. Ammonia is recognized as a cell toxicant in higher animals and the reduction of the amount which the intestinal epithelial cells are exposed to, could lead to a reduction of epithelial turnover, a sparing of energy and a better nutrient utilization. In other words, the ability of Natural Cellular Defense to trap ammonium ions allows for a less toxic digestive tract and better overall nutrient uptake from food and supplements.

The best known positive biological activity of natural zeolite is its action as an anti-diarrheal drug. Zeolites lower the incidence of death and sickness (diarrheal syndrome) produced by intestinal diseases in swine, rats, and calves. Based on these results a comprehensive study was carried out on anti-diarrheal drugs based on natural zeolite as an active material, in the therapy of acute diarrheal diseases in humans. The research led to approval of the anti-diarrheal drug Enterex for use in humans

Peroral use of encapsulated zeolite powders enriched with vitamins, oligoelements or other ingredients has been claimed to exert beneficial medical effects. Ingestion of zeolites may be considered analogous to the clay eating (geophagia), considered in traditional medicine as a remedy for various illnesses. The bulk of ingested zeolite probably remains undissolved in the gut. In view of the ion exchange properties, zeolites may be expected to change the ionic content, pH and buffering capacity of the gastrointestinal secretions and to affect the transport through the intestinal epithelium. In addition, zeolites could affect the bacterial flora and the resorption of bacterial products, vitamins and oligoelements. The contact of zeolite particles with gastrointestinal mucosa may elicit the secretion of cytokines with local and systemic actions. This creates a healthier digestive tract with beneficial microflora and microfauna.

8. Immune system modulation

Accumulating evidence has indicated that zeolites play an important role in regulating the immune system. Several studies have reported that silica, silicates, and aluminosilicates act as nonspecific immunostimulators similarly to superantigens. Superantigens are a class of immunostimulatory and disease-causing proteins of bacterial and viral origin with the ability to activate relatively large fractions (5–20%) of the T cell population. Activation requires simultaneous interaction of the superantigens with V-domain of T cell receptor and with major histocompatibility complex class II molecules on the surface of antigen presenting cells. Proinflammatory macrophages, which belong to class II MHC antigen-presenting cells, are activated by fibrogenic silicate particulates. Indeed, experiments have shown that removal of MHC class II DP/DR positive cells results in a lack of macrophage stimulation by asbestos. Direct interaction of silicate particles with cells other than lymphocytes has also been identified and described. It seems that mineral particles can trigger alterations in gene expression by initiating signaling events upstream of gene transactivation. Exposure of cells to silicate particles has been shown to lead to activation of mitogen-activated protein kinases (MAPK), protein kinase C, and stress-activated protein kinases. Important transcription factors such as activator protein 1 and nuclear factor B are also activated, and expression of proinflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor is enhanced. Modifications in receptor activation kinetics or activity of integrins may be responsible for the observed behavior

The aim of one study was to evaluate the antiviral properties of a natural non-toxic zeolite. Herein, a fine powder of micronized zeolite (MZ) was obtained. Different viral suspensions were treated with MZ in concentrations ranging from 0.5 to 50 mg/ml. The viral proliferation was evaluated by optical microscope as percentage of cytopathic effect (CPE). Human adenovirus 5, herpes simplex virus type 1 (HSV 1) and human enteroviruses (coxsackievirus B5 and echovirus 7) were used in the antiviral assay. Concentrations of 0.5 and 5 mg/ml of MZ induced a very low antiviral effect or the antiviral was not observed at all, while concentrations of 12, 25 and 50 mg/ml of MZ induced a significant inhibitory effect upon viral proliferation. MZ inhibited the viral proliferation of HSV 1, coxsackievirus B5 and echovirus 7 more efficiently than adenovirus 5. The antiviral effect of MZ seems to be non-specific and is more likely based on the incorporation of viral particles into pores of MZ aggregates than ion exchange properties of the zeolite. Preliminary results indicate a possibility of therapeutic application of MZ, either locally (skin) against herpesvirus infections or orally in cases of adenovirus or enterovirus infections.

The aim of a prospective, open, and controlled parallel-group study was to investigate the effects of supplementation with another zeolite on the cellular immune system in patients undergoing treatment for immunodeficiency disorder. A total of 61 patients were administered daily zeolite doses for 6 to 8 weeks, during which the patients' primary medical therapy was continued unchanged. Blood and lymphocyte counts were performed at baseline and at the end of the study. Blood count parameters were not relevantly affected in either of the two treatment groups. Zeolite administration resulted in significantly increased CD4+,

CD19+, and HLA-DR+ lymphocyte counts and a significantly decreased CD56+ cell count. No adverse reactions to the treatments were observed.

9. Safety and Tolerability

Food additives and supplements in the U.S.A. are approved by the Food and Drug Administration (FDA) under the Code of Federal Regulations (CFR) Title 21. Zeolites (CFR Title 21 (182.2727)) and Sodium Magnesium or Aluminum Silicates under CFR Title 21 (182.2227) are listed as GRAS (Generally Recognized as Safe), and are permitted as food additives (supplements) without FDA approval. Furthermore, all ingredients (zeolites) are found on the TSCA listing of GRAS chemicals used in every day commerce in the United States.

10. Appendix 1 - References:

Aikoh T, Tomokuni A, Matsukii T, Hyodoh F, Ueki H, Otsuki T, Ueki A (1998) Activation-induced cell death in human peripheral blood lymphocytes after stimulation with silicate in vitro. Int J Oncol 12:1355–1359

Bedioui F (1995) Zeolite-encapsulated and clay-intercalated metal porphyrin, phthalocyanine and Schiff-base complexes as models for biomimetic oxidation catalysts: an overview. Coordination Chem Rev 144:39–68

Breck DW (1964) Crystalline molecular sieves. J Chem Educ 41:678–689

Cheshmedzhiev, B.V.,Angelov,A.,Nestorov,N., Bakalivanov, S., Cheshmedzhieva, R. (1985) Effect of zeolite in the feeding of pregnant and nursing sows and sucking piglets. Zhivotnov `'dni Nauki 22, 40-46 (abstract)

Chinery R, Brockman JA, Peeler MO, Shyr Y, Beauchamp RD, Coffey RJ (1997) Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer-a p53 independent induction of p21WAF1/CIP1 via C/EBPβ. Nat Med 3: 1233–1241

Ci olic´ M, Pavelic´ K (2000) Molecular mechanisms of anticancer activity of some natural dietetic products. J Mol Med 78:333–336

Coffey, M. T & Pilkington, D. W. (1989) Effect of feeding Zeolite-A on the performance and carcass quality of swine. Journal of Animal Science 67 (Supplement 2), 36 (abstract)

Colella C (1999) Natural zeolites in environmentally friendly processes and applications. Stud Surface Sci Catalysis 125:641–655

Concepcion-Rosabal B, Rodriguez-Fuentes G, Simon-Carballo R (1997) Development and featuring of the zeolitic active principle FZ: a glucose adsorbent. Zeolites 19:47–50

EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS (1998) Guideline On Good Clinical Practices. EMEA/CVMP/595/98: London, UK

Flanigen EM (1980) Molecular sieve zeolite technology-the first twenty-five years. In: Rees LVC (ed) Proceedings of the5th International Conference on Zeolites. Heyden, London, pp 760–780

Garces JM (1999) Observations on zeolite applications. In: Treacz MMJ, Marcus BK, Misher ME, Higgins JB (eds) Proceedings of the 12th International Conference on Zeolites. Materials Research Society, Warrendale, pp 551–566

Harvey, R. B., Kubena, L. F., Elissalde, M. H. & Phillips, T. D. (1993) Efficacy of zeolitic ore compounds on the toxicity of aflatoxin to growing broiler chickens. Avian Diseases 37, 67-73

Lopez, R. G., Elias, A. & Menchaca, M. A. (1992) The utilization of zeolite by dairy cows. 2. Effect on milk yield. Cuban Journal of Agriculture Science 26, 131-134

Ma, C. S., Tzeng, C. M., Lai, M. K. & Tsai, A. H. (1979) Effect of zeolite feeding of pregnant pigs on the litter size at birth. K'o Hseuh Nung Yeh (Taipei) 27, 189-192

Ma, C. S., Yang, S. K., Tzeng, C. M. & Wu, H. K. (1984) Effect of feeding clinoptilolite on embryo survival in swine. In: Zeo-Agriculture. Use of Natural Zeolites in Agriculture and Aquaculture. Eds W. G., Pond & F. A., Mumpton. Boulder, Colorado: Westview Press Inc., pp. 155-160

Martin LD, Krunkosky TM, Dye JA, Fischer BM, Jiang NF, Rochelle LG, Akley NJ, Dreher KL, Adler KB (1997) The role of reactive oxygen and nitrogen species in the response of airway epithelium to particulates. Environ Health Perspect 105 [Suppl 5]:1301–1307

Meier, M.W., Siegmann, K., 1999. Signi.cant reduction of carcinogenic compounds in tobacco smoke by the use of zeolite catalysts. Microporous Mesoporous Mater. 33, 307–310.

Metaxas, M., Kasseloui-Rigopoulou, V., Galitsatou, P., Konstantopoulou, C., Oikonomou, D., 2003. Thorium removal by different adsorbents. J. Hazard. Mater. B 97, 71–82.

Miazzo, R., Rosa, C. A., De Queiroz Carvalho, E. C., Magnoli, C., Chiacchiera, S. M., Palacio, G., Saenz, M., Kikot, A., Basaldella, E. & Dalcero, A. (2000) Efficacy of synthetic zeolite to reduce the toxicity of aflatoxin in broiler chicks. Poultry Science 79, 1-6

Mirvish, S.S., 1983. The etiology of gastric cancer: introgastric nitrosamide formation and other theories. J. Natl. Cancer Inst. 71, 629–647.

Mitchell, P.C.H., 1991. Zeolite-encapsulated metal complexes: biomimetic catalysts. Chem. Ind., 308–311.

Mumpton, F. A. (1984) Natural zeolites. In: Zeo-Agriculture. Use of Natural Zeolites in Agriculture and Aquaculture. Eds W. G., Pond & F. A., Mumpton. Boulder, Colorado: Westview Press Inc., pp. 33-44

Mumpton, F. A. & Fishman, P. H. (1977) The application of natural zeolites in animal science and aquaculture. Journal of Animal Science 45, 1188-1203

Naber JE, De Jong KP, Stork WHJ, Kuipers HPCE, Post MFM (1994) Industrial application of zeolite catalysis. Stud Surface Sci Catalysis 84C:2197–2220

Namasivayam, C., Kadiverlu, K., 1997. Agricultural solid wastes for the removal of heavy metals: adsorption of Cu(II) by coirpith carbon. Chemosphere 34, 377–399.

Olver, M. D. (1997) Effect of feeding clinoptilolite (zeolite) on the performance of three strains of laying hens. British Poultry Science 38, 220-222

Pearson, G., Smith, W. C. & Fox, J. M. (1985) Influence of dietary zeolite on pig performance over the liveweight range 25±87 kg. New Zealand Journal of Experimental Agriculture 13, 151-154

Pond, W. G. & Yen, J. T. (1983) Reproduction and progeny growth in rats fed clinoptilolite in the presence or absence of dietary cadmium. Bulletin of Environmental Contamination Toxicology 31, 666-672

Pond, W. G., Yen, J. T. & Varel, V. H. (1988) Response of growing swine to dietary copper and clinoptilolite supplementation. Nutrition Reports International 37, 797-803

Rabo, J.A., Angell, C.L., Kasai, P.H., Schomaker, V., 1966. Studies of cations in zeolites: adsorption of carbon monoxide; formation of Ni ion and Na3þ 4 centers. Discuss. Faraday Soc. 41, 328–349.

Ramos, A. J., Fink-Gremmels, J. & Hernandez, E. (1996a) Prevention of toxic effects of mycotoxins by means of nonnutritive adsorbent compounds. Journal of Food Protection 59, 631-641

Ramos, A. J., Hernandez, E., Pla-Delfina, J. M. & Merino, M. (1996b) Intestinal adsorption of zearalenone and in vitro study of nonnutritive sorbent materials. International Journal of Pharmacology 128, 129-137

R.M. Barer, Zeolites and Clay Minerals as Sorbent and Molecular Sieves, Academic Press, New York, 1987.

Rodriguez-Fuentes G, Barrios MA, Iraizoz A, Perdomo I, Cedre B (1997) Enterex – anti-diarrheic drug based on purified natural clinoptilolite. Zeolites 19:441–448

Roussel, J. D., Thibodeaux, J. K., Adkinson, R. W., Toups, G. M. & Goodeaux, L. L. (1992) Effect of feeding various levels of sodium zeolite A on milk yield, milk composition and blood profiles in thermally stressed Holstein cows. International Journal of Vitamin and Nutrition Research 62, 91-98

Sersale R (1985) Natural zeolites: processing, present and possible applications. Stud Surface Sci Catalysis 24:503–512

Shurson, G. C., Ku, P. K., Miller, E. R. & Yokohama, M. T. (1984) Effects of zeolite A or clinoptilolite in diets of growing swine. Journal of Animal Science 59, 1536-1545

Smith, T. K. (1980) Effect of dietary protein, alfalfa, and zeolite on excretory patterns of 50,5 0,7 0,7 0-[3H] zearalenone in rats. Canadian Journal of Physiology and Pharmacology 58, 1251-1255

Ueki A, Yamaguchi M, Ueki H, Watanabe Y, Ohsawa G, Kinugawa K, Kawakami Y, Hyodoh F (1994) Polyclonal human T-cell activation by silicate in vitro. Immunology 82: 332–335

Wang, Y., Zhu, J.H., Yan, D., Huang, W.Y., Ma, L.L., 2001. Adsorption of N-nitrosamines by zeolites in solutions. Stud. Surf. Sci. Catal. 135, 226.

Weiner, H.C., 1997. Oral tolerance: immune mechanisms and treatment of autoimmune diseases. Immunol. Today 18, 335–343.

Xu, Y., Wang, Y., Zhu, J.H., Ma, L.L., Liu, L., 2002. Progress in the application of zeolite in the life science: novel additive for cigarette to remove N-nitrosamines in smoke. Stud. Surf. Sci. Catal. 142, 1489–1496.

Xu, Y., Yun, Z.-Y., Zhu, J.H., Xu, J.-H., Liu, H.-D., Wei, Y.-L., Hui, K.-J., 2003a. Trapping volatile nitrosamines with the copper incorporated zeolites. Chem. Commun., 1894–1895.

Xu, Y., Zhu, J.H., Ma, L.L., Ji, A., Wei, Y.L., Shang, X.Y., 2003b. Removing nitrosamines from main-stream smoke of cigarette by zeolite. Microporous Mesoporous Mater. 60, 125–137.

Yannakopoulos, A., Tserveni-Gousi, A., Kassolifournaraki, A., Tsirambides, A., Michailidis, K., Filippidis, A., Lutat, U. (2000) Effects of dietary clinoptilolite-rich tuff on the performance of growing-finishing pigs. In: Natural Zeolites for the Third Millenium. Eds C., Coela & F.A., Mumpton. Napoli, Italy: De Frede Editore, pp. 471-481

Zhu, J.H., Yan, D., Xia, J.R., Ma, L.L., Shen, B., 2001. Attempt to adsorb N-nitrosamines in solution by use of zeolites. Chemosphere 44, 949–956.