Technical information for healthcare professionals

# TECHNICAL INFORMATION

Gold-standard study

## Research PMA-Zeolite®

(PMA – PANACEO-Micro-Activation)

Study summary and explanation of the mechanism of action and the main intended effect

PANACEO

# Contents





# PANACEO introduces itself.

Welcome to PANACEO, your specialist for natural solutions to promote intestinal health.

### PMA-Zeolite® – The foundation stone for intestinal health

Our PMA-Zeolite® is the result of intensive research and development work. With its unique ability to selectively bind harmful substances and at the same time release essential minerals and trace elements, PMA-Zeolite® optimizes the intestinal environment and sustainably strengthens the barrier function of the intestinal wall. It offers a fundamental solution for many intestinal problems and can contribute to effective and holistic intestinal rehabilitation as a basic therapeutic agent.

As the market leader in the human application of the natural ion exchanger, we at PANACEO are committed to the meticulous research and continuous optimization of our natural active ingredient. This process includes everything from the careful selection and extraction of the raw material to patented processing and comprehensive research into possible medical applications. The specially developed PMA-Zeolite® is used specifically to provide support where increased intestinal permeability or intestinal auto-intoxication leads to a deterioration in well-being or to associated inflammatory disease.

In this brochure, we present information on the role of the intestinal wall barrier, insights into our research methods and the results of our extensive research and development work. It covers a broad spectrum from *in vitro* studies to *in vivo* studies and placebo-controlled, double-blind studies and highlights both primary and secondary effects that PMA-Zeolite® from PANACEO can have in your therapeutic practice.

**NOTE:** The studies cited in this specialist information were carried out with the certified medical product PMA-Zeolite®. The PMA technology is a patented process in which the biophysical properties are altered. [25] This means that the following findings are not transferable to other zeolite-clinoptilolite products.

## PANACEO medical devices are certified Class IIb medical devices based on the unique PMA-Zeolite®

(in accordance with Directive 93/42 EEC - recognizable by the CE mark on the product)

QM certification in accordance with the EN ISO 13485:2016 standard is also in place. This **guarantees the safety, homogeneity, usability and effectiveness of the products.**

## European patents

protect the **innovative know-how** and **uniqueness** of PANACEO products.

## Pure material

As the starting substance is a **naturally occurring mineral,** the **quality** is crucial for medical success. As with any naturally occurring substance, the natural composition of zeolite-clinoptilolite varies depending on where and how it is formed.

As a manufacturer of medical products based on zeolite-clinoptilolite, it is our responsibility to ensure quality and safety for our users. A European zeolite source personally evaluated by us provides us with the best and purest raw material. An exclusive contract guarantees that the high-quality zeolite-clinoptilolite, which is extracted using a gentle and environmentally friendly mining method, is supplied exclusively to PANACEO as the basis for PMA-Zeolite®. This raw material quality is significantly higher than the average material that is otherwise frequently used.

## Research and development

In the field of research and development, PANACEO cooperates with European institutes and universities and renowned opinion leaders.

## Unique technology optimizes effectiveness

**The PMA process technology from PANACEO is a globally unique process** in which the particles of zeolite-clinoptilolite are crushed under the influence of very high kinetic energies. In addition to a modification of the crystal lattice, this leads to an even **stronger surface charge and thus to significantly higher effectiveness.** [1, 2, 3]

The spherical, highly fissured particles have an optimized (because enlarged) outer surface and an average grain size of around three to five thousandths of a millimeter (5 µm). The calculation of the surface area of the PMA-Zeolite® by the Vienna University of Technology has shown that with a total penetration depth into the pores, 1 gram of the active ingredient produced by PANACEO has an effective surface area of around 4,000 square meters.4 Differences in the absorption behavior arise primarily in the pH value of the environment. PMA-Zeolite® shows optimum absorption capacity in the human digestive tract.

## Easy to use

Take 1 measuring spoon of powder or 3 capsules **2 – 3 times a day** with a glass of water (at least 100 ml). The duration of the treatment should be at least 12 weeks or as long as the recurring physical stresses are present.

## Made in Austria

As a traditional, Austrian family-run company, we offer our customers the highest quality and the best service and innovative power.



# Initial situation

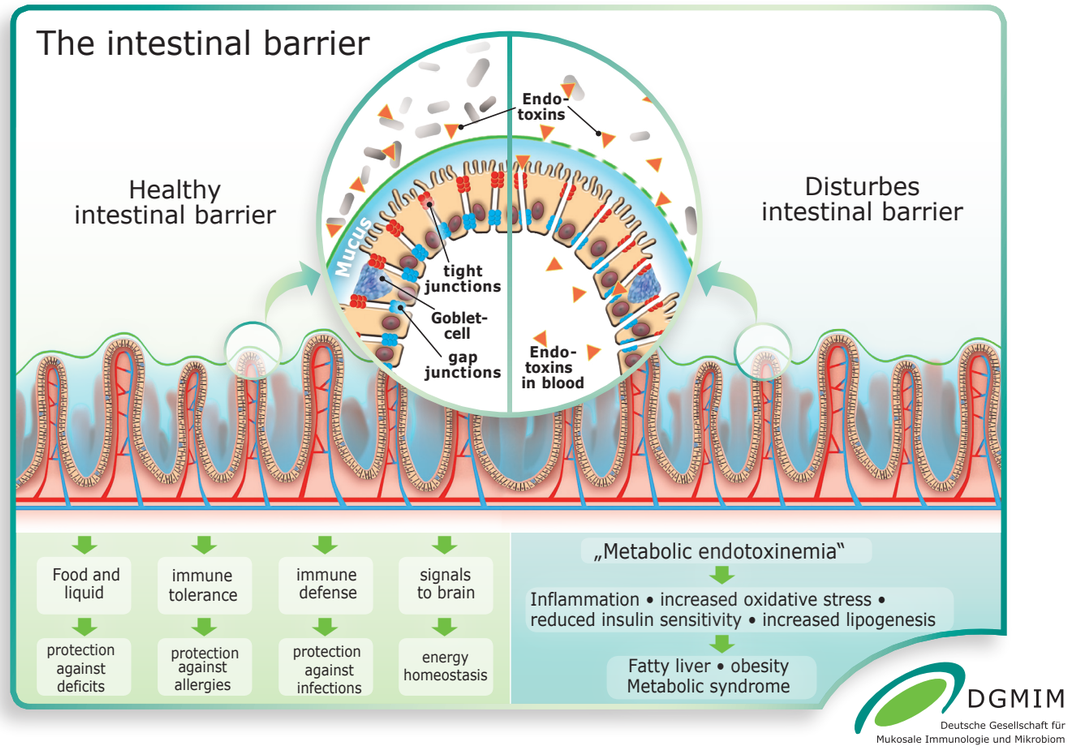


Figure 1: Illustration of the healthy and dysfunctional intestinal barrier including its functions and the effects of dysfunctions. [5]

## The role of the intestinal wall barrier for health

The intestine does not only play an essential role in the digestive process, but also protects the human organism from harmful substances through its function as a semi-permeable membrane and performs numerous immunological functions. It is therefore the most important barrier to prevent the penetration of foreign substances. The protective intestinal wall serves as a mechanical barrier and works with the intestinal immune system and its defense cells to maintain a balance of messenger substances, hormones, protective secretions and degrading enzymes. An intact intestinal wall function is therefore an essential prerequisite for health.

## The role of environmental pollution for health

According to the World Health Organization (WHO), environmental pollutants are still responsible for up to a quarter of all diseases and deaths in Europe, despite considerable progress in environment and health in recent decades. [6] Environmental hazards in Europe are responsible for around 26 % of all ischemic heart diseases, 25 % of all strokes and 17 % of all carcinomas. [56] In recent years, it has become increasingly clear that some diseases occur more frequently than originally suspected due to the chronic accumulation of environmental pollutants, especially heavy metals.[7] Many of these pollutants (such as cadmium or lead) can accumulate in the soil even at low concentrations and are subsequently able to accumulate in the food chain, both on land and in water. [8] As a result, the European Rapid Alert System for Food and Feed (RASFF) [9] continuously detects excessive concentrations of environmental pollutants in our food. Environmental physician Hans-Peter Hutter (in an interview with Martin Schriebl-Rümmele, environmental journalist) [10] also confirms that the greatest environmental burdens are usually invisible to us and therefore receive too little attention.

## Lifestyle

The EPIC Norfolk Prospective Population Study, a British human study with 20,000 subjects, confirms the clear impact of a healthy lifestyle compared to an unhealthy lifestyle. The parameters for maintaining health were smoking, exercise, alcohol consumption and diet. The significant difference in life expectancy between the test subjects with a healthy and unhealthy lifestyle is 14 years on average.[11]

Since not all risk factors can be eliminated by lifestyle changes, it is essential to strengthen the gastrointestinal tract (GIT) as the largest interface between humans and the outside world, including its immunological function. The intestinal epithelium or the intestinal wall is an essential part of the GIT that can be damaged by various stresses. Chronic diseases, medication, nutrition (e.g. gluten) or noxious substances from the environment (e.g. heavy metals) can impair the intestinal wall or make it unphysiologically permeable.[48] In the literature, this is referred to as increased intestinal permeability or leaky gut.

**A study analysis [49] identified two main areas of leaky gut:**

- The loss of intestinal barrier function in connection with autoimmunological processes. [55] Research, particularly about the valid biomarker zonulin is growing. Zonulin levels are shown to be elevated in the development of coeliac disease (gluten is one of the strongest triggers), type 1 diabetes or drug therapies as well as other stressors from food and psychological and physical stress.
- Bacterial translocation (= increased entry of bacteria or bacterial products into the bloodstream) as the pathophysiological mechanism. In the case of incorrect or reduced intestinal microflora, an imbalance can lead to dysbiosis (unfavorable distribution of desired/undesired bacteria), which can destabilize the intestinal mucosa. [50]

**Recent evidence-based publications confirm the following connections to leaky gut:**

- Irritable bowel syndrome (with diarrhea) [12]
- Inflammatory bowel diseases [13] (e.g. ulcerative colitis, Crohn's disease)
- Allergies [14]
- Food intolerances [15]

**Intestinal-associated complaints/diseases:**

- Autoimmune diseases [16]
- Frequent infections or immunodeficiency [17]
- Exhaustion due to illness [18]
- Non-alcoholic fatty liver [19]
- Neurodermatitis, psoriasis, acne [20, 21]

## Dual mechanism of action of PMA-Zeolite®

The main effect and the mechanism of action of PMA-Zeolite® are scientifically proven. The PMA-Zeolite® tackles the root of the problem by repairing the damaged intestinal wall and binding harmful substances.

- Strengthening of the intestinal wall barrier (significant decrease in zonulin $p < 0.05$) and tendency towards an anti-inflammatory effect (slight increase in the cytokine IL10, $p < 0.1$). [22]
- Reduction of pollutants such as lead, cadmium, arsenic, chromium, and nickel [23] as well as ammonium in the gastrointestinal environment. [24]

## Why PMA-Zeolite® from PANACEO

As safety and efficacy are of paramount importance, preclinical and clinical studies have been commissioned since 1999, as already mentioned at the beginning.

Thanks to ongoing development and research, PMA-Zeolite® has valid scientific evidence of increased effectiveness, with the greatest possible safety - guaranteed, tested, checked and permanently monitored.



# Research and Development

## The research focus

Our research focuses on intestinal health, in particular the protective function of the intestinal wall.

In addition to its role in digestion, the intestine plays an essential role in immune defense as the body's largest immune organ. Around 80 % of active immune cells are located under the intestine's huge surface.

If the intestinal wall loses its natural protective and filtering function, this is referred to as "leaky gut". As a result, more undesirable substances (e.g. bacteria components) can enter the body's circulation from the intestine, which not only affect the intestine itself (= local inflammatory reactions) but also the immune system and downstream organs (= systemic inflammatory reactions). This is referred to as endotoxemia.

As gut health can have an impact on various organs, science is increasingly focusing on the so-called gut-body axes.

The research focus of PANACEO is therefore the effect of PMA-Zeolite® on the intestine and the integrity of the intestinal wall (leaky gut) and its effects on our organism and the associated pathologies. This is illustrated by the gut-body axes.

### Gut-body axes

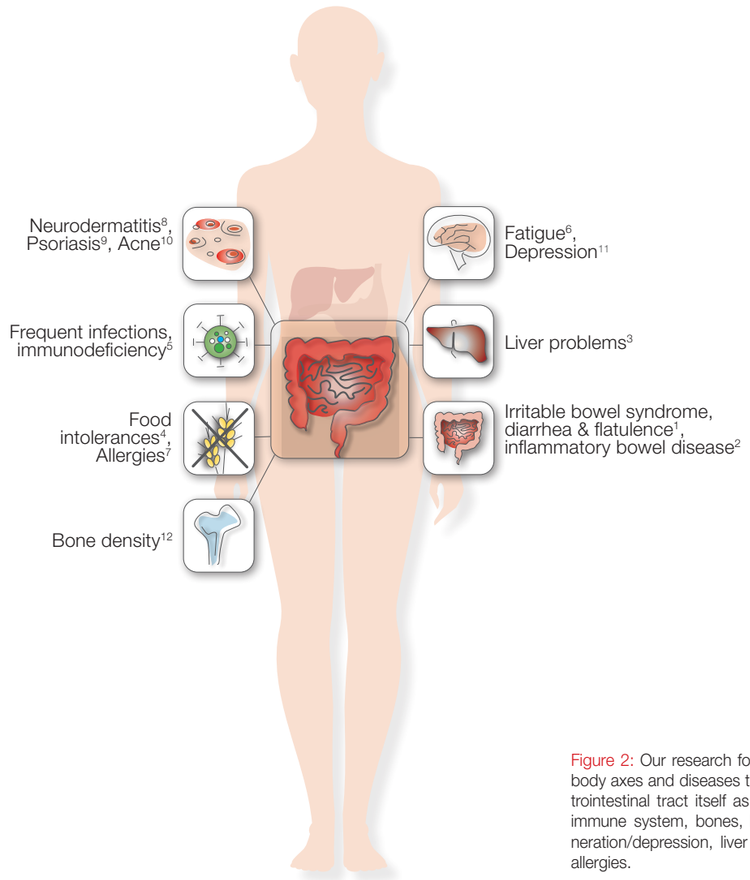


Figure 2: Our research focuses on the gut-body axes and diseases that affect the gastrointestinal tract itself as well as: the skin, immune system, bones, brain, neurodegeneration/depression, liver and intolerances/allergies.


1 Gecse K et al. (2012)
2 Chang J et al. (2017)
3 Saltzmann ET et al. (2018)
4 Leccioli V et al. (2017)
5 Nalle SC and Turner JR (2015)
6 Morris G et al. (2016)
7 Mansueto P et al. (2015)
8 Craig JM (2016)
9 Pietrzak et al. (2017)
10 Lee YB et al. (2019)
11 Calarge CA et al. (2019)
12 Pavelic Kraljevic S et al. (2020)

## The current research focus:

Research results from PANACEO confirm the natural support of intestinal health in the following areas:

- Leaky gut and accompanying factors such as irritable bowel syndrome or elevated liver values
- Better tolerability of drug therapies
- Supporting the bone metabolism (osteoporosis)
- Pollutant prevention
- Supporting physical performance/resilience through a strong gut

## Milestones in our research

All subsequent studies and evidence on the use of the products were carried out with our own active ingredient, known as PMA-Zeolite®, and are exclusively attributable to this active ingredient. For this reason, we refer to our optimized PMA-Zeolite® as the "original".

**from 2000 until 2007**

**Thoma, W. (2006):** Clinical observation of the use of activated zeolite (= PMA-Zeolite®) since April 2000

**Knapitsch, Schmölzer, (2004):** Randomized double-blind placebo-controlled study with PANACEO Sport on lactate levels and performance improvement

**Thoma, Gunzer, (2006) Clinical observation:** The antioxidant effect of active volcanic mineral zeolite (PMA-Zeolite®) on the oxidative system

**Abuja, P.M. (2006):** An investigation of the antioxidant activities of PANACEO

**Schulz, N., (2007):** Practical report on the use of the preparation PANACEO MED in the context of irritable bowel syndrome since 2004

**until 2011**

**Bachl, N., (2011):** Evaluation of the results of a randomised, double-blind study with PANACEO Sport to assess the effect on physical performance parameters

**Thoma, (2011):** Clinical Observation of Administration of PANACEO MED (Representative Sample of Patients)

**Triebnig, (2011):** Activated natural zeolite clinoptilolite in complementary medicine. Proven Roborans for severe diseases, recommended adjuvant for chemotherapy and radiotherapy. (Note: Evaluation of 150 representative patient files from a long-term application observation of over 2,000 patients in the form of documented medical cases over a period of 10 years using PMA-Zeolite®.

**2012**

**Weber D., (2012):** Study on the use of zeolite in the adjuvant treatment of eating disorders in particular with regard to the BMI and liver and kidney parameters

**2013**

**Oberwinkler (2013):** Influence of activated (modified) natural zeolite-clinoptilolite to relieve the liver (GPT, GOT, y-GT)

**2015**

**Lamprecht et al., (2015):** Effects of zeolite supplementation on parameters of intestinal barrier integrity, inflammation, redoxbiology and performance in aerobically trained subjects

**2016**

**Pavelić, Pavelić Kraljevic and Simović (2016):** Effect of PMA-Zeolite-clinoptilolite® on the mineral metabolism and selected blood parameters



**2017 until 2018**

**Pavelić, Kraljevic and Pavelić, (2017):** Effect of a PMA-Zeolite-clinoptilolite® on selected contaminants (heavy metals) after long term supplementation – safety evaluation

**Pavelic Kraljevic et al., (2017):** Novel, oxygenated clinoptilolite material efficiently removes aluminium from aluminium chloride-intoxicated rats in vivo. Microporous and Mesoporous Materials 249

**Pavelic Kraljevic et al., (2018):** Critical Review on Zeolite Clinoptilolite Safety and Medical Applications in vivo. Front. Pharmacol., 27 November 2018 | https://doi.org/10.3389/fphar.2018.01350

**2020 until 2021**

**Vitale et al., (2020):** ZeOxaNMulti Trial: A Randomized, Double-Blinded, Placebo-Controlled Trial of Oral PMA-Zeolite® to prevent Chemotherapy-Induced Side Effects, in particular, Peripheral Neuropathy

**Böhm et al., (2020):** Progress in health management through innovative diagnostics: The interpretation of ellipsoid erythrocytes under the dark field microscope in connection with Leaky Gut and the influence of PMA-Zeolite® on the blood environment and the intestinal barrier

**Eisenwagen S and Pavelić K. (2020):** Potential Role of Zeolites in Rehabilitation of Cancer Patients. Archives of Physiotherapy and Rehabilitation 3: 029-040

**Pavelić, Kraljevic et al., (2020):** Treatment of osteoporosis with a modified zeolite shows beneficial effects in an osteoporotic rat model and a human clinical trial. Experimental Biology and Medicine. Vol 246, Issue 5, 2021

**Petkov, V. et al., (2021):** PMA-Zeolite® can ameliorate inflammation in patients with irritable bowel syndrome – a randomized, double blinded, controlled pilot trial Running head: PMA-Zeolite® and IBS (Irritable Bowel Syndrome). Neuro Endocrinol Lett . 2021 Mar;42(1):1-12

**2022**

**Kraljević Pavelić, S. et al. (2022):** Clinical Evaluation of a Defined Zeolite-Clinoptilolite Supplementation Effect on the Selected Blood Parameters of Patients. Front. Med., 27 May 2022; Sec. Pathology

**Kraljević Pavelić, S. et al. (2022):** Clinical Parameters in Osteoporosis Patients Supplemented With PMA-Zeolite® at the End of 5-Year Double-Blinded Clinical Trial. Frontiers in Medicine. 9:870962. doi: 10.3389/fmed.2022.870962

**Vitale, M.G. et al. (2022):** Survival analyses of the ZeOxaNMulti trial: Follow-up randomized, double-blinded, placebo-controlled trial of oral PMA-Zeolite® to prevent chemotherapy-induced side effects, especially peripheral neuropathy. Front. Pharmacol., 08 November 2022 Sec. Drugs Outcomes Research and Policies. https://doi.org/10.3389/fphar.2022.874028

**2023**

**Dolanc I, et al. (2023):** The Impact of Long-Term Clinoptilolite Administration on the Concentration Profile of Metals in Rodent Organisms. Biology (Basel). 2023 Jan 26;12(2):193. doi: 10.3390/biology12020193

**2024**

**Mosgoeller, W. et al. (2024)** 'PMA-Zeolite® (Clinoptilolite) in the Management of Irritable Bowel Syndrome – a Non-Interventional Study', Zeitschrift für Gastroenterologie [Preprint]. https://doi.org/10.1055/A-2223-3963

## Methodology of the studies and proof of efficacy

In order to comply with the regulations and specifications of a certified medical device and to ensure maximum safety and efficacy for the end user, numerous studies are systematically carried out.

**1. Studies on the product safety/toxicology**

▼

**2. Studies on the dual mechanism of action**
2.1. Strengthening of the intestinal wall barrier (Gold-Standard Study)
2.2. Binding of pathogenic substances in the GIT (*in vitro*)

▼

**3. Studies on the plausibility of secondary effects**
3.1. Human studies
3.2. *In vivo* and *in vitro* studiesn

Figure 2: Simplified representation of the development phases for study planning and implementation.

# Summary of studies

## 1. Product safety / toxicology studies

### Background information / Objective

The essential basis for the safety aspects to be fulfilled for certified Class IIb medical devices, is permanent research activities. Safety must be checked based on the relevant standards. All safety-relevant, independent studies are carried out with the PMA-Zeolite® manufactured / processed by PANACEO.

### Method

Physical as well as chemical material characterization and toxicological tests were carried out.

### Physical and chemical material characterization

First and foremost, the chemical and physical characterization of the specific PMA-Zeolite® is a fundamental component. These features are essentially characterized by its composition (physical / chemical / mineralogical), as well as by the selectivity series and particle properties (round and no needle-shaped particles) and must be presented accordingly.

**Three important features for the safety of PMA-Zeolite® human application:**

- Testing the stability against acids and alkalis (pH 1.2 - 11),
- and high temperature stability (up to 450 °C) have been confirmed. The stability is therefore given under physiological conditions in the gastrointestinal tract (the site of action of PMA-Zeolite®).
- Another important quality feature regarding chemical composition is the clinoptilolite content of
- > 80 % and a correspondingly high silicon to aluminum ratio (> 5:1). Further quality parameters for PMA-Zeolite® are the clearly defined selectivity series, which indicates which pollutants (cations) are particularly easily absorbed and exchanged for physiological cations (Mg, Ca, K, Na, ...). More detailed information on material characterization and the physical principle of action is summarized in the final analysis.

### Toxicological tests

The assessment of safety includes tests for cytotoxicity, sensitization, irritation, subchronic toxicity and genotoxicity.

To provide additional safety, further toxicology data are also available.

### Results

- **Cytotoxicity**

The results on cytotoxicity show that the extracts of the samples do not cause any critical biological damage to the test cells and can therefore be classified as non-cytotoxic.

- **Sensitization and irritation**

Testing for irritation and sensitization also shows that the products do not cause toxic or allergic reactions.

- **Subchronic toxicity**

Continuous long-term use, with a dosage many times higher than the recommended dose stated on the products, is safe.

- **Genotoxicity**

These tests prove that the products are not mutagenic.

A review published in 2018 documents the safe medical use of the specific PMA-Zeolite®. In addition, this review explicitly points out that no generally valid statement can be made about all clinoptilolite minerals, as they differ significantly due to various processing methods. The assessment can only be made depending on the study situation of the respective mineral. [25]

## Conclusion

After several evaluations of the safety-relevant aspects, both the designated notified body and experts confirmed the safety of PMA-Zeolite® in human applications. Based on expert opinions, tests and studies (physical and chemical material characterization as well as toxicological tests), in which *in vitro* and *in vivo* results mutually confirm each other, the active ingredient PMA-Zeolite® and the medical products developed from it can be classified as safe for the human organism.

# 2. Studies on the dual mechanism of action

## 2 . 1 Strengthening of the intestinal wall barrier [22]

### Introduction and background

Under the direction of PD DDr. Manfred Lamprecht, this clinical randomized study was carried out at the Institute for Nutrient Research and Sports Nutrition - Green Beat - and the Institute of Physiological Chemistry at the Medical University of Graz from December 2012 to July 2014 in accordance with the gold standard. It investigated the effect of PMA-Zeolite® on the intestinal barrier, inflammation levels, redox biology and performance in physically stressed adults.

### Methods

The test subjects were 52 healthy, endurance trained men and women aged 20 – 50 years who, after a wash-out phase from all dietary supplements and sports supplements, started a 12-week supplementation with the medical product PMA-Zeolite® (approx. 2 g/day) or with a placebo. Stool and blood analyses were taken after 0 and 12 weeks of supplementation to determine the defined biomarkers and parameters.

All test subjects were monitored regarding the intestinal wall barrier to assess stress-induced leaky gut syndrome. It is known that different types of stress, particularly physical stress, can lead to a disruption of the intestinal wall function (leaky gut syndrome). A test subject clientele of endurance trained people was therefore used. The effects of PMA-Zeolite® on the intestinal wall permeability and integrity of the tight junctions were investigated using the enterotoxin zonulin (a valid biomarker for intestinal wall integrity/ permeability). Other parameters such as anti-inflammatory cytokines and membrane proteins as well as a mineral panel were also evaluated.

**Explanations ZONULIN:**

The regulatory protein zonulin is a suitable marker for measuring the permeability of the intestinal epithelium or intestinal wall. Zonulin regulates the exchange of fluid, macromolecules and leukocytes between the bloodstream and the intestinal lumen. It also protects the subepithelial layers. Various stimuli cause the intestinal epithelial cells to release zonulin into the intestinal lumen and blood vessels. Examples include direct contact with bacteria in the absence or interruption of the intestinal mucus layer and contact with gliadin.

Zonulin docks onto the receptors on the surface of the intestinal epithelial cells and triggers a signaling cascade that causes the cytoskeleton of the cell to contract. As a result, the tight junctions open. If the zonulin-mediated opening of the tight junctions is repeated and intensified, the so-called leaky gut develops. [26]

### Results

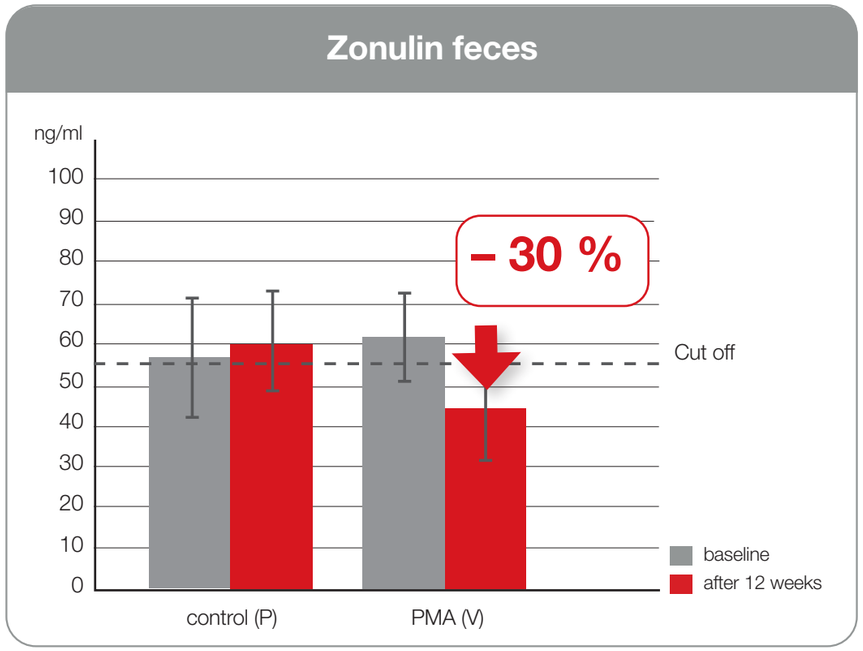


**Figure 4:** Zonulin concentration in stool in the verum and placebo groups after 0 and 12 weeks of supplementation. Values are mean ± SD, $p < 0.05$ (ANOVA), n = 27 (verum), n = 25 (placebo).

| Parameters / Biomarker | Result | Interpretation |
|---|---|---|
| Zonulin | significant change (decrease) ($p < 0.05$) | At the beginning, both groups showed consistently elevated zonulin values (> 30 ng/mL) above the norm in stool. This is an indication of impaired permeability of the intestinal epithelium and is correlated with intestinal wall permeability disorders.<br>After supplementation for 12 weeks, a significant reduction in the faecal zonulin levels ($p<0.05$) was documented in the verum group compared to the control group, in which there were almost no changes. |
| IL-10 (Interleukin 10) | Trend ($p<0.1$) | The summary result of the measurement of membrane proteins and anti-inflammatory cytokines after a supplementation period of 12 weeks is a slight increase in anti-inflammatory cytokines (IL-10 - immunomodulator in the intestinal tract). This means that an anti-inflammatory tendency has been determined. |
| Other parameters (e.g. mineral panel) | no significant change | At the beginning and end of the supplementation, no significant differences between the treatment and placebo groups were detected. |

**Table 1:** Summarized results from the Lamprecht gold standard study

The summarized results from Table 1 show a significant decrease in the biomarker **zonulin (p < 0.05)** and an anti-inflammatory **tendency (p < 0.1).** This means that in the population group studied (people with a stress-induced disorder of the barrier function of the intestinal wall), supplementation with PMA-Zeolite® resulted in a faster normalization and resumption of intestinal wall function. The slight anti-inflammatory tendency (p < 0.1) supports and relieves the immune system.

In connection with leaky gut, it should be noted that various clinical pictures, including irritable bowel syndrome (with diarrhea), are associated with this symptom. Dr. Norbert Schulz carried out an observational study and documented good success in the use of PMA-Zeolite® on irritable bowel syndrome in patients who had undergone inpatient regeneration cures. [27]

### Conclusion

The strengthening of the intestinal wall integrity as a protective barrier of the body is the main output from this placebo-controlled, randomized double blind, gold standard study. The anti-inflammatory effect should also be positively emphasized.

The purpose of using PMA-Zeolite® is to alleviate an intestinal wall dysfunction as an injury to the intestinal wall or to relieve/strengthen the intestinal wall. This can lead to an alleviation of the symptoms of "leaky gut" and any associated chronic inflammation or related clinical pictures.

The target group are adults who are exposed to repeated physical stress. These are regularly stressful everyday lifestyles and living conditions - i.e.: little sleep/bad diet/stress... the daily repetition of these circumstances leads to stress on our gastrointestinal tract.

## 2 . 2 Binding of pathogenic substances in the GIT [23, 24]

**Selective binding of heavy metals and ammonium by acting as a cation exchanger**

### Introduction and background

Once safety has been proven, it is essential to demonstrate the mechanism of action according to the ion exchange capacity at the site of action (gastrointestinal tract).

### Methods

To maintain the natural stomach and intestinal environment (pH value), test solutions were prepared and mixed with the substances to be tested (lead, cadmium, arsenic, chromium, nickel and ammonium). The test was carried out by adding PMA-Zeolite® in doses of up to 3 g. The heavy metal and ammonium concentrations were measured using sensitive measurement methods.

### Results

The result is optimal binding (and consequently elimination) of lead in the stomach model (low pH value - acidic environment) and lead, cadmium, arsenic, chromium and nickel in the intestinal model (higher pH value - alkaline environment).

The ammonium reduction in the gastrointestinal environment increases in relation to the amount of PMA-Zeolite®. At a dosage of 3 g PMA-Zeolite® (= approx. 1 portion spoon of powder), the reduction is approx. 60 %.

### Conclusion

The key is the selective physical binding of certain harmful substances in the gastrointestinal tract, which means that these substances can no longer damage the body. The fact that the reduction of heavy metal exposure has a positive physiological effect on the human body has been confirmed by a panel of experts from the European Food Safety Authority (EFSA). [28]

**Prof. DDr. Krešimir Pavelić**

*„In our research we have seen that the natural zeolite-clinoptilolite has outstanding properties and opens up new possibilities in the field of biology and medicine.“*

## 3. Studies addressing plausibility of secondary effects

Based on the dual mechanism of action of PMA-Zeolite® and its positive effects on the intestine and downstream organ systems, the plausibility of secondary effects was also investigated and scientifically explained.

## 3.1. Human studies

### 3.1.1. PANACEO in irritable bowel syndrome patients (pilot study) [57]

### Introduction and background

Irritable bowel syndrome (IBS) is a functional bowel disorder that is often difficult to diagnose and remains undetected for a long time. Those affected often go through a long period of suffering, which is associated with psychosomatic elements and subclinical inflammation that can potentially be traced back to food intolerances. 20 years of preclinical and clinical research have shown that PMA-Zeolite® binds and reduces irritating chemical components and can therefore alleviate low-grade mucosal irritation as experienced by IBS patients.

### Method

A prospective, controlled, double-blind, randomized pilot study was conducted with 41 diagnosed IBS patients. The participants received either 3 g of PMA-Zeolite® (verum) or microcrystalline cellulose (placebo) orally twice daily. At baseline and after three months, symptom burden, blood and stool inflammation parameters such as high-sensitivity C-reactive protein (hsCRP), zonulin, $\alpha$1-antitrypsin, interleukin IL-10 and changes in the gut microbiome were determined.

### Result

The IBS-associated symptom values decreased significantly in both groups (p=0.001), which indicates a strong placebo effect. This is not unusual, as the gut is very strongly connected to the psyche through the gut-brain axis. In the PMA-Zeolite® group, various inflammation-associated parameters (including microbiome species such as Lactobacillus, Bifidobacteria, Firmicutes) showed synergistic shifts; the statistical comparison with the placebo group showed significantly improved **α1-antitrypsin** level (p = 0.037).

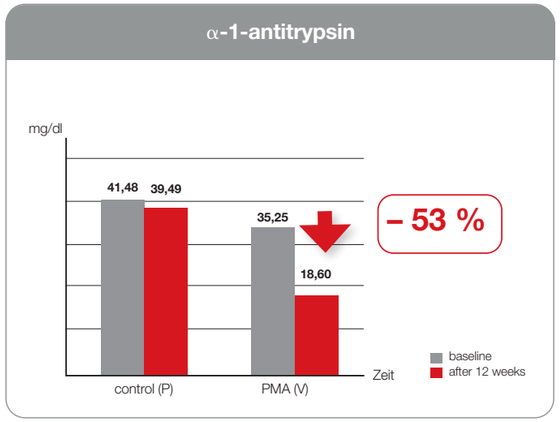


**Figure 5:** α-1-antitrypsin in stool (mg/dl) at the beginning of the pilot study (=baseline) and after 12 weeks. The mean value is significantly reduced in the verum group compared to the placebo group (p = 0.037).

### Conclusion

The decrease in hsCRP in blood and stool as well as $\alpha$1-antitrypsin indicates that PMA-Zeolite® can alleviate subclinical inflammation and improve the integrity of the intestinal mucosa in IBS patients. The parallel increase of the immune-modulating species Bifidobacterium and Lactobacillus and the reduction of Firmicutes could further contribute to the anti-inflammatory effect. The data suggest further research into PMA- Zeolite® in IBD patients with pronounced signs of inflammation.

### 3.1.2. Treatment of irritable bowel syndrome (non-interventional study) [58]

#### Introduction and background

Based on the positive results of the pilot study described above, this non-interventional study (NIS), which was conducted throughout Austria since July 2019. The aim was to document the tolerability and efficacy of PMA-Zeolite® under everyday conditions in patients with diarrhea-like IBS type (IBS-D), constipation type (IBS-C) or mixed type (IBS-M).

#### Methods

As part of the NIS, **204 patients** (¾ female and ¼ male) **with IBS** were recruited to collect data on tolerability, quality of life and symptom frequency. The study focused on **IBS-related quality of life (measured using the SF-36 questionnaire)** and improvements in IBS-related **symptoms according to the IBS-specific ROM-III criteria,** as well as stool consistency (measured using the **Bristol Stool Form Scale).**
The participants documented their symptoms such as abdominal pain and flatulence, as well as the number of bowel movements and stool consistency via a web-based internet platform before and after taking (initial and exit questionnaires) 2 portion spoons of PMA-Zeolite® per day and kept an analog diary over the intake period of 8 weeks.

#### Results

82.2 % of the recruited patients had completed the questionnaires before and after the 8-week treatment with PMA-Zeolite®.

- Seven of the eight subscales of the **SF-36** improved significantly (p<0.001),
- the **reduction in abdominal pain** was also significant (p<0.001).
- The analyses of the diary entries confirmed the **reduction in abdominal pain** and showed a **significant decrease in the number of days with flatulence.**
- The Bristol stool form analysis showed improvements. **Patients with IBS-D particularly benefited from the treatment (p < 0.001).**

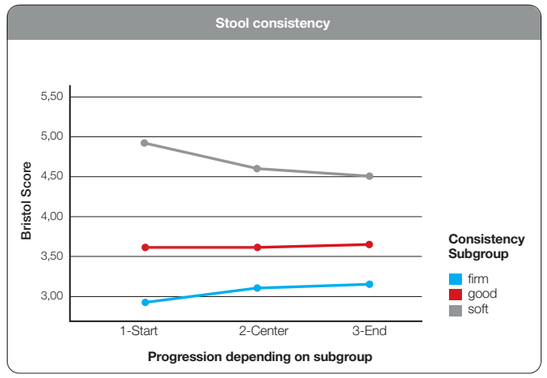


**Figure 6:**
Stool consistency over the course of the study depending on the initial consistency. The groups - "too soft" type and "too firm" type -benefit from taking PMA-Zeolite®. The curves approach the ideal value.

#### Conclusion

Under everyday conditions, PMA-Zeolite® alleviated the global IBS-related symptoms and improved the disease-associated quality of life. PMA-Zeolite® could be a good adjuvant therapy option for patients with irritable bowel syndrome.

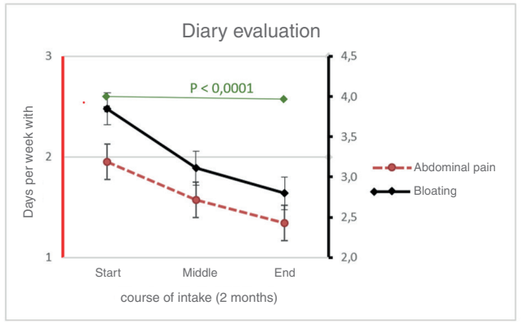


**Figure 7:**
The number of days with abdominal pain or flatulence decreases while taking PMA-Zeolite®.

### 3.1.3. The treatment of osteoporosis with a modified Zeolite® shows positive effects in an osteoporotic rat model and a clinical study in humans.[59]

#### Introduction and background

Osteoporosis has become a widespread disease and since the results of our previous *in vivo* study were positive, we conducted a randomized, double-blind, placebo-controlled human clinical trial to investigate the use of PMA-Zeolite® as a possible alternative or adjuvant treatment option in the therapy of osteoporosis.
The severity of osteoporosis manifests in its high incidence and complications, which reduce the quality of life.
PMA-Zeolite® could therefore represent a further treatment option. PMA-Zeolite® acts in and via the gastrointestinal tract. The barrier function of the intestinal endothelium is essential to prevent antigens from crossing this barrier and causing pro-inflammatory effects that can ultimately lead to bone loss.

#### Methods

This is a randomized, double-blind, placebo-controlled study with 100 subjects: Osteoporosis patients, 6 male, 94 female, BMD-T score below 2.5; patients were untreated or had discontinued standard therapy. Exclusion of severe diseases such as cancer, autoimmune diseases, chronic kidney failure and secondary osteoporosis or pregnancy. All female participants had postmenopausal osteoporosis.

50 subjects verum, 50 subjects placebo

- **Randomization:** in two groups: Verum (PMA-Zeolite®) (n = 50) or placebo/control group (microcrystalline cellulose) (n = 50). The subjects were instructed to maintain their daily diet and lifestyle during the study. Restriction on the intake of medication and food supplements; exception: vitamin D3 (800 IU).
- **Intake and duration:** 12 months and dose verum/placebo of 3 x 1 level portion spoon powder/day, taking into account the time interval to other medications.
- **Compliance:** Subjects were contacted every three months for a complete examination and health check, as well as for motivation and adherence to the protocol.
- **Parameters:** Subjects were monitored at baseline, 6 months and 12 months. The markers were indicators of bone formation or bone preservation:
    - Assessment of **BMD** (bone mineral density) as a function of time;
    - Changes in **osteocalcin concentration** (marker for bone formation);
    - Changes in **beta(β)-cross-laps** (marker for bone resorption);
    - **Pain: VAS** - Visual Analog Scale (scale from 1 - 5) and subjective assessment of health quality.

#### Results

Patients treated with PMA-Zeolite® showed a significant increase in bone mineral density ($p < 0.001$), a significantly increased level of markers that indicate bone formation (osteocalcin; $p = 0.001$) and a significant reduction in markers for bone resorption (Beta-Cross-Laps; $p = 0.027$). Furthermore, there was a significant reduction in pain and a significantly improved quality of life compared to patients in the control group (placebo).

#### Conclusion

These and other studies from a well-founded literature research **(Charité Berlin)** show that treatment with PMA-Zeolite® can have a positive effect on bone metabolism and bone density due to its effect in the gastrointestinal tract and on the intestinal wall barrier.

## **3.1.4.** Clinical Parameters in Osteoporosis Patients Supplemented with PMA-Zeolite® at the End of 5-Year Double-Blinded Clinical Trial. [60]

### Introduction and background

This follow-up study on osteoporosis is based on the results of our one-year, randomized, doubleblind, placebo-controlled TOP1 (Treatment of Osteoporosis) study (Ref.: Fachinformation F&E_010_Osteoporose_V001). This 1-year study was continued over a total period of 5 years. All subjects who took placebo in the first year were switched to taking PMA-Zeolite®. The results of the long-term use of PMA-Zeolite® over a period of 4 or 5 years are described and discussed in the summary below.

We specifically observed the effects of PMA-Zeolite® on the parameters of bone quality – more precisely bone mineral density (BMD), osteocalcin, beta-cross-laps-Ctx, fracture risk and quality of life in a cohort of 55 osteoporosis patients (originally: 100 patients).

### Methods

This is a randomized, double-blind, placebo-controlled study with 100 subjects: Osteoporosis patients, 6 male, 94 female, BMD-T score below 2.5; patients were untreated or had discontinued standard therapy. Exclusion of severe diseases such as cancer, autoimmune diseases, chronic kidney failure and secondary osteoporosis as well as pregnant women. All female participants had post-menopausal osteoporosis.

- **Randomization (for 1 year, then pear control):** in two groups: Verum (PMA- Zeolite®) (n = 50) or placebo/control group (microcrystalline cellulose) (n = 50). After the 1st year, the placebo group was discontinued; all test subjects received PMA-Zeolite® (verum group) for the remaining years (4 or 5 years in total).
- **Dosage and duration:** For 12 months, the dosage was verum/placebo 3 x 3 g powder/day. The intake took place at breakfast, lunch and dinner, taking into account the time interval to other medications for a further 4 or 5 years, all test persons took only the PMA-Zeolite® 3 x 3 g powder/day. The test subjects were instructed to maintain their daily diet and lifestyle during the study. Restriction on the intake of medication and food supplements; exception: vitamin D3 (800 IU).
- **Compliance:** Subjects were contacted every three months for a complete examination and health check, as well as for motivation and compliance with the protocol.
- **Parameters:** The subjects were monitored at the start of the study, after 6 months, after 12 months and every 3 months for motivation purposes (study duration 60 months in total). The markers were indicators of bone metabolism:
    - o **Fracture** as a parameter of quality of life: Quality of life was assessed based on the presence of fractures, the occurrence of falls and the level of pain at the beginning, during and at the end of the study. Fractures were documented five years before and during the study period.
    - o Changes in **osteocalcin concentration** (marker for bone formation);
    - o Changes in the **beta-cross laps** (marker for bone resorption);
    - o Assessment of **BMD** (bone mineral density) as a function of time;
    - o **Pain: VAS** - visual analog scale (scale of 1 - 5) and subjective assessment of health quality. At the beginning and end of the 5-year TOP study.

### Results

Patients treated with PMA-Zeolite® showed improved regenerative bone quality over the course of the study, in the 5-year TOP study:

The increased osteocalcin and reduced Beta-Cross-Laps values showed a preference for the bone formation process ($p < 0.05$).

Bone mineral density (BMD) was not significantly affected after the 5-year follow-up in patients treated with PMA-Zeolite®. This indicates balanced bone remodeling (or new bone formation), which is important for bone homeostasis and is lacking in long-term pharmacological treatment of osteoporosis.

The development of fractures, which was measured as a parameter of quality of life is of particular interest. Patients treated with PMA-Zeolite® suffered less fractures in relation to the number of falls ($p = 0.002$) compared to the period of 5 years before entry into the study.

Finally, the subjective perception of pain (VAS) also decreased significantly when treated with PMA-Zeolite® ($p < 0.001$), while the perception of overall health improved significantly ($p < 0.001$).

### Conclusion

These and other studies from a well-founded literature research **(Charité Berlin)** show that treatment with PMA-Zeolite® can have a positive effect on bone metabolism and bone density due to its effect in the gastrointestinal tract and on the intestinal wall barrier.

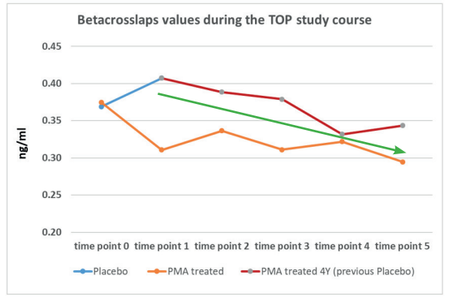


**Figure 8:**
The Beta-Cross-Laps values (marker for bone resorption) decrease significantly over the course of the study.

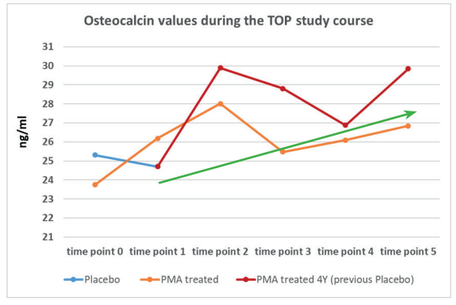


**Figure 9:**
The osteocalcin values (marker for bone formation) increase significantly over the course of the study.

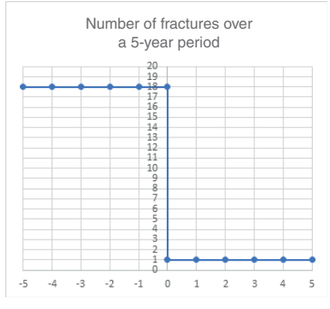


**Figure 10:**
The number of fractures decreases drastically over the course of the study.

### 3.1.5. Clinical study on the reduction of chemotherapy-induced side effects with PMA-Zeolite® [61]

#### Introduction and background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of oncological therapies - including the chemotherapeutic agent oxaliplatin. In the present study, the possible adjuvant use of PMA-Zeolite® in oxaliplatin therapies was investigated. The effect of PMA-Zeolite® is based on its ability to selectively ad/absorb toxic substances in the gastrointestinal tract, such as heavy metals (lead, cadmium, arsenic, chromium, nickel) and ammonium. Ammonium has a neurotoxic effect and is produced by tumors.

#### Methods

This is a randomized, double-blind, placebo-controlled study initiated by AORN Antonio Cardarelli, Department of Medical Oncology, Naples, Italy. It comprises 120 patients with colorectal carcinoma, 66 males, of which 35 placebo and 31 verum; 54 females, of which 25 placebo and 29 verum. Study duration from April 2015 to October 2018 (3.5 years)

- **Chemotherapeutic agent:** oxaliplatin derivatives (highly neurotoxic), adjuvant, first or second line
- **Randomization:** verum (PANACEO MED) or placebo (microcrystalline cellulose)
- **Administration and duration:** a total of 7 months - administration/placebo of 2 x 3 g/day during and up to 1 month after completion of chemotherapy, taking into account the time interval to other drugs and discontinuation for two days before and after therapy a total of 7 months - administration/placebo of 2 x 3 g/day during and up to 1 month after completion of chemotherapy, taking into account the time interval to other drugs and discontinuation for two days before and after therapy
- **Measurement of nerve conduction velocity (NCS):** before the start of administration, after 3 and 6 months
- **Parameters:** CIPN, hematologic toxicity, hepatotoxicity during the chemotherapy cycle

#### Results

Interestingly, in the subgroup of men, those subjects who received PMA-Zeolite® showed significantly lower CIPN (p = 0.047) compared to the placebo group. In the subgroup of women, on the other hand, there was no difference between verum and placebo group in relation to the CIPN (p = 0,43). Furthermore, a statistically significant improvement in compliance (fewer treatment discontinuations) was achieved with PMA-Zeolite® treatment (p = 0.03). In addition, there was a trend towards a lower incidence of severe hematologic toxicity (p = 0.09) in the verum group. No statistical analysis was performed on liver toxicity (hepatotoxicity), as no hepatotoxicity was observed in 111 patients.

#### Conclusion

Oncology patients may benefit from therapy with PMA-Zeolite® in terms of CIPN. The lower CIPN, with statistically significant results in the male subgroup, was associated with a trend towards a lower incidence of severe hematologic toxicity. PMA-Zeolite® treatment also resulted in better tolerability of chemotherapy (increase in cycles) and better adherence to the oncological treatment protocol.

### 3.1.6. Follow-up study with PMA-Zeolite® to prevent chemotherapy-related side effects, especially peripheral neuropathy [62]

#### Introduction and background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of oncological therapies - including the chemotherapeutic agent oxaliplatin. In the present study, the possible adjuvant use of PMA-Zeolite® in oxaliplatin therapies was investigated. The effect of PMA-Zeolite® is based on its ability to selectively ad/absorb toxic substances such as heavy metals (lead, cadmium, arsenic, chromium, nickel) and ammonium in the gastrointestinal tract. Ammonium a neurotoxic effect and is produced by tumors.

#### Methods

A sample size of 104 colorectal cancer patients (52 % of participants randomized to the PMA-Zeolite® group and 48 % to the placebo group) out of a total of 120 patients enrolled in the ZeOxaNMulti study in 2015 completed follow-up by March 2021 and were included in the follow-up analysis. Depending on the chemotherapy line, 44.2 % of patients received chemotherapy in an adjuvant setting and 55.8 % of patients in the first-line treatment. The statistical analysis for DFS (disease-free survival), PFS (progression-free survival) and OS (overall survival) was performed with the start of the PMA-Zeolite®/Placebo intervention as the starting point.

#### Results

The analyses showed a relevant trend towards improved OS for first-line patients taking PMA-Zeolite® (p = 0.1) over the entire follow-up period (= 30 months). After 7 months of PMA-Zeolite® use, first-line chemotherapy patients in the verum group showed significantly improved OS compared to the placebo group (p = 0.004). A borderline statistical significance was also achieved for PFS when taking PMA-Zeolite® (7 months) for cancer progression events in patients undergoing first-line treatment (p = 0.05).

#### Conclusion

Based on this analysis, possible concerns regarding a reduced efficacy of chemotherapy can be dispelled and a protective effect of PMA Zeolite® supplementation can be demonstrated. A positive trend or even significant results in PFS and OS for certain patient groups during and/or after PMA-Zeolite® treatment were observed and support the use of PMA-Zeolite® as an additional oncological therapy.

## **3.1.7.** Effect of PMA-Zeolite® on selected blood parameters of patients

### Introduction and background

Zeolite clinoptilolite is a natural mineral with a stable base of aluminum and silicon. It acts as an ion exchanger, releasing more than 30 bound minerals and trace elements into the body and binding heavy metals due to its high affinity to various pollutants. Although the natural mineral is used extensively in industry, veterinary and human medicine, there is little data on the influence of zeolite supplementation on the concentration of physiologically relevant minerals in the human organism.

### Methods

A comprehensive and controlled monitoring of the relevant mineral and pollutant concentrations in persons with and without PMA-Zeolite® treatment from three clinical studies was carried out. The effect of PMA-Zeolite® treatment on certain mineral and heavy metal concentrations in plasma was determined using standard biochemical methods and inductively coupled plasma mass spectrometry (ICP-MS). The test subjects from the following three clinical studies with different treatment protocols were used for this purpose:

1. **Short-term treatment** of healthy adults with 6 g/day over **28 days.** n = 15, of which 8 subjects had already started taking PMA-Zeolite® at least 6 months before the start of the study ("chronic" group). 7 subjects started taking it at the start of the study ("naive" group). Measured parameters: Na, K, Zn, Mg, Ca and pollutants (mineral metabolism and certain blood parameter study - MMBP).

2. **Medium-term treatment** of patients diagnosed with Crohn's disease under standard therapy with 6 g/day over **12 weeks.** n = 40, of which 30 patients with uncontrolled Crohn's disease were treated with placebo (15 patients) or PMA-Zeolite® (15 patients). 10 healthy subjects served as controls and received placebo (5 subjects) or PMA-Zeolite® (5 subjects). Measured parameters: Na, K, Cl, Fe, Mg, and Ca and pollutants. (Crohn's disease study).

3. **Long-term treatment** of osteoporosis patients without or after discontinuation of standard therapy with 9 g/day over **4 years.** n = 100, of which 50 patients were treated with placebo and 50 patients with PMA-Zeolite®. The study was completed by 62 subjects. Measured parameters: P, Ca, mineral and pollutant concentrations. (Osteoporosis TOP study).

### Results

After short-term treatment with PMA-Zeolite® for 28 days ("naive" group, MMPB study), an increased lead (Pb) concentration was observed compared to the long-term treated subjects ("chronic" group), which was, however, within the reference range.

In the Crohn's disease study, a significantly reduced arsenic (As) concentration was measured in the serum of the test subjects after 12 weeks of taking PMA-Zeolite®.

In the osteoporosis study, initially reduced copper (Cu) concentrations were observed in the PMA-Zeolite®-treated test subjects, which normalized again over the course of the study. The sodium (Na) and calcium (Ca) concentrations as well as the concentrations of lead (Pb), nickel (Ni) and aluminum (Al) were significantly reduced in the PMA-Zeolite®-treated group compared to the plaque group.

### Conclusion

In this study, it was shown that the arsenic (As) concentration was significantly reduced after just 12 weeks of PMA-Zeolite® intake.

The long-term treatment in the osteoporosis study showed significantly reduced sodium (Na), calcium (Ca), lead (Pb), nickel (Ni) and aluminum (Al) concentrations with PMA-Zeolite® intake. The changes in Na, Ca and Pb concentrations in osteoporosis patients are attributed in the study to the bone remodeling process.

After one year of PMA-Zeolite® supplementation, the Cu, Ca and Na concentrations should be checked.

In summary, this work speaks for the safety of the long-term intake of PMA-Zeolite®.



## **3.1.8.** Austria-wide plausibility study - Intestinal & liver relief [29]

### Introduction and background

The aim was to prove that the oral intake of PMA-Zeolite® has a positive influence on the liver values aspartate aminotransferase (AST or formerly known as GOT), alanine aminotransferase (ALT or formerly GPT) and gamma(γ)-glutamyltransferase (-GT or GGT) and thus relieves the liver.

### Methods

The Austrian pilot study started in fall 2013 in collaboration with general practitioners, clinics and internists with a total group size of 130 test subjects with elevated liver values for a wide variety of deliberately unspecified causes. The treatment took place over a period of 1 - 3 months and a dosage of 2 x 1 portion spoon of PANACEO MED per day. Only the blood parameters ALT, AST and -GT were measured before the start and at the end of the test interval and used to evaluate the success of the therapy.

### Results

The evaluation showed a significant reduction in ALT, AST and γ-GT activities in more than 2/3 of all test subjects after the intake period. The documented reduction in enzyme activity indicates that elevated liver parameters can be lowered naturally, without further pharmacological stress. This positive result was unforeseeable, especially since neither inclusion nor exclusion criteria, or compliance were defined or checked in more detail.

### Conclusion

Due to the central importance of a functioning intestinal wall barrier, strengthening it could represent a positive supportive approach for patients with clinical pictures which, according to scientific literature, are associated with a leaky gut.

This plausibility study was able to document that PMA-Zeolite® has a positive effect on liver detoxification through its action via the gut-liver axis. According to scientific outputs, a leaky gut and a disturbed gut immune system as well as an impaired microbiome are key factors for disturbances of the gut-liver axis. [45]

In addition, an observational study was conducted on treatment with PMA-Zeolite® during therapy for people with alcohol problems (2021). Here, a positive influence of PMA-Zeolite® treatment on the decrease in the key parameter GGT (gamma-glutamyl transferase) was observed. The observation also indicates a positive effect regarding quality of life and well-being. These data suggest that taking PMA-Zeolite® has a positive effect on the liver. [64]

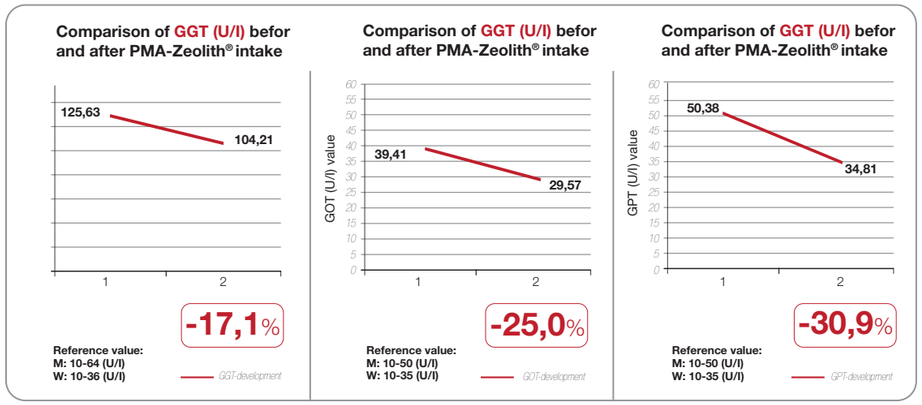


**Figure 11:** A significant reduction in liver enzyme values was detected in 2/3 of the patients, which indicates an improvement in liver health (representation based on median value).

## **3.1.9.** Human studies - improvement of liver and kidney parameters in eating disorders [30]

### Introduction and background

This plausibility study was conducted in 2012 under the direction of clinical psychologist Dr. Dieter Weber and Dr. Gustav Raimann at the Paracelsus health resort in Villach. The aim was to prove that PMA-Zeolite® has a positive influence on the viand nutrient intake as well as kidney parameters and liver values of bulimia and anorexia nervosa patients.

### Methods

The framework of this plausibility study, conducted in a parallel group design, was an inpatient therapy for different forms of eating disorders (n = 21). The duration of supplementation took place in two treatment groups and was at least 5 weeks inpatient and 6 months outpatient. With an identical treatment method and adherence to a strict therapy plan, one treatment group (11 people) received one level measuring spoon (= approx. 3 g) of PMA-Zeolite® mixed with a little water three times a day with their main meals, while the control group (10 people) ate their meals without supplementation. As part of the treatment, various blood parameters (for immune defense, liver, kidney, digestion, fat metabolism) as well as body measurements and bowel movements were recorded.

### Results

The study results, which were evaluated blindly, show that the BMI of the verum group improved significantly by over 30% compared to the reference group. Furthermore, a significant improvement in the measured liver enzymes (GPT, GOT and γ-GT) and a reduction in the kidney parameter (creatinine) was documented in the verum group. Elevated values may indicate renal insufficiency. The significant reduction in cholesterol levels in the verum group should also be mentioned.

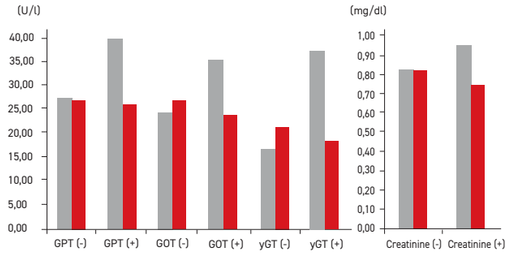


**Figure 12:**
Summary of the measured liver and kidney values. The data showed that treatment with PMA-Zeolite® induced a significant reduction in the markers.

**Summarized explanation of the measured parameters (Figure 12):**

**GPT (glutamate pyruvate transaminase), now known as ALT (alanine aminotransferase):**

As a result of the treatment, the verum group shows a reduction in the GPT level of approx. 50 %, which means a return to the optimal range. In comparison, the GPT-levels in the control group remained constant.

**GOT (glutamate oxaloacetate transaminase), now known as AST (aspartate aminotransferase):**

Elevated values in the verum group decreased during therapy and normalized. In contrast, a slight increase in values was observed in the control group.

**γ-GT (gamma-glutamyltransferase):**

Before the therapy, the γ-GT values in the verum group were in the upper range of the limit values. Afterwards, the parameter was reduced by 50 %. In comparison, the control group showed a slight increase in values.

**Creatinine:**

Supplementation with PMA-Zeolite® resulted in a significant reduction in creatinine in the verum group, while it stayed constantly high in the control group.

### Conclusion

Oral intake of PMA-Zeolite® resulted in an improvement in liver and kidney parameters compared to the reference group. This is caused by the strengthening of the intestinal wall function, the anti-inflammatory effect [22] and the selective binding of harmful substances. [23, 24, 31] By relieving the digestive organs, it can also be explained that an improvement in the absorption of vital substances and nutrients is possible. This may also explain the increase in BMI in the PANACEO group in this study. The improvement in cholesterol levels can also be explained by the liver relief. The data collected is consistent with the findings of the preclinical study on liver regeneration capacity.



## **3.1.10.** Increase in antioxidant capacity [32]

### Introduction and background

The gastrointestinal tract in particular (defined area of action of PMA-Zeolite®) is exposed to a range of pathogenic substances (e.g. heavy metals). Zeolite can counteract this burden through its selective ion exchange capabilities.
Among other things, heavy metal ions are counteracted by free cations (Na+, K+, $Ca^{2}$+, $Mg^{2}$+) stored in the zeolite and thereby exchanged. The basic research studies cited below show that PMA-Zeolite® not only reduces heavy metal ions but also transition metal ions, which contribute to the formation of free radicals. Likewise, as described below, the release of specific ions (as coenzymes) supports the body's own antioxidant system. In this way, the organism can be protected from oxidative damage. The aim of this observational study was to examine the effect of PMA-Zeolite® on the oxidative system and to assess the resulting significance for the immune system.

### Methods

The group of participants (22 healthy people) took 3 x 3 capsules or 3 x 2 teaspoons of the powder daily. In two measurements before and after the oral application of PMA-Zeolite®, the hydroperoxides (= waste products in the oxidation process) in the capillary blood were determined using the Free Radical Analytical System (FRAS) and the unit of measurement U.Carr. (=Carratelli units). 1 U.Carr. corresponds to 0.08 mg/dl $H_2O_2$. The normal value is 250 to 300 U.Carr. and is equivalent to 20 to 24 mg/dl $H_2O_2$. The concentration of hydroperoxides corresponds to the free radicals in the blood. Free radicals are problematic because they damage the cell through oxidation.

### Conclusion

According to the study leader, the average reduction was very high. In over 100 studies with various other antioxidants, no comparable reduction in free radical levels was found. The basis for this documented effect is the effect of PMA-Zeolite® in the gastrointestinal tract. Based on preclinical data, it is hypothesized that the physical mechanism of action as an ion exchanger reduces transition metal ions, that contribute to the formation of free radicals.

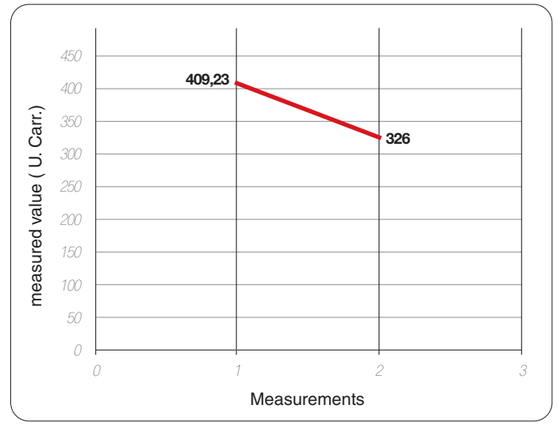


**Figure 13:** In the pre-post comparison, supplementation with PMA-Zeolite® resulted in an average reduction of 83 U.Carr. in 22 participants. The reduction results from the average values of the 1st measurement (U.Carr. = 409) compared to the second measurement (U.Carr. = 326).

### **3.1.11.** Increasing antioxidant capacities in physically stressed people. [33, 34]

#### Introduction and background

The current randomized, placebo-controlled, double-blind study in humans, which was evaluated by Prof. Bachl and conducted by Dr. Knapitsch on 24 test subjects, is also related to the positive effects on the body's own antioxidant system from the observational study described above.

#### Methods

The supplementation period took place over a period of two weeks and a dosage of 3 x 3 capsules per day after the initial examination or after taking 12 capsules and 30 minutes before exercise (ergometry) on test days. This procedure was the same in both the vehicle and placebo groups. The heart rate and lactate levels in the blood were defined as success parameters.

#### Results

A slower increase in blood lactate concentration was measured in the treatment group compared to the placebo group. The lactate reduction had decreased significantly ($p < 0.005$) or even highly significantly ($p < 0.001$) in the verum group after one week (T2) or two weeks (T3) compared to the initial value (T1) (see Table 2). In contrast, there was a slight increase in lactate levels in the placebo group (not significant).

#### Conclusion

The documented reduction in lactate concentrations may be due to the effect of PMA-Zeolite® as an enzyme promoter. Through the release of trace elements (as co-factors) there is a connection to caboanhydrase. This is an enzyme and has a direct influence on the $CO_2$ metabolism. Thus, a connection to lactate reduction and an effect on the body's own antioxidant system can be established.

The basis of this secondary effect (antioxidant effect of PMA-Zeolite®) is always the main mechanism of action of zeolite clinoptilolite, namely the targeted reduction of pathogenic substances in the gastrointestinal environment. This also includes the physical reduction of transition metal ions, which contribute to the formation of free radicals. The body's own antioxidant enzymes can be supported thanks to the trace elements (co-factors) supplied via the ion exchange, which in turn leads to a reduction in free radicals.

This reduction in turn means that more oxygen remains in the muscle, thereby inducing a shift from anaerobic to aerobic performance (= reduction in lactate levels at the same load). This effect ultimately relieves the body as an assumed systemic secondary effect, which causes a release of energy that would otherwise be required for the breakdown of the stressful substances and cell repair processes.

| Verum (N=12) | (T1) | | (T2) | | (T3) | |
|---|---|---|---|---|---|---|
| km/h at 2mml/l | 10,32 | ± 2,59 | 11,39* | ± 2,94 | 11,70** | ± 2,88 |
| km/h at 3mml/l | 12,13 | ± 2,86 | 13,12* | ± 2,98 | 13,39** | ± 2,84 |
| km/h at 4mml/l | 13,27 | ± 2,89 | 14,21* | ± 3,04 | 14,58** | ± 2,82 |

| Placebo (N=11) | (T1) | | (T2) | | (T3) | |
|---|---|---|---|---|---|---|
| km/h at 2mml/l | 11,74 | ± 2,15 | 11,44 | ± 2,00 | 11,83 | ± 2,00 |
| km/h at 3mml/l | 13,29 | ± 2,10 | 13,35 | ± 1,88 | 13,45 | ± 2,01 |
| km/h at 4mml/l | 14,36 | ± 1,99 | 14,37 | ± 1,98 | 14,40 | ± 2,10 |

**Table 2:** Statistics lactate reduction of T2 and T3 against T1: * $p < 0.005$ (T2 to T1) and ** $p < 0.001$ (T3 to T1)



## **3.2.** *In vivo* and *in vitro* studies

### **3.2.1.** Review of the safety of zeolite clinoptilolite and its *in vivo* medical applications [65]

#### Use of clinoptilolite in veterinary and human medicine:

As an **ion exchanger** with **adsorption capacity,** clinoptinolite has great potential for use in veterinary and human medicine. Due to its **high affinity for** the pollutant **ammonium**, it is often used in animal feed and fertilizers.

This ability is of particular interest in human medicine, as ammonium is a toxic end product of protein metabolism. It has been shown to have negative effects on the intestinal microbiome and the health of the intestinal mucosa. Excessive ammonium production can be caused by diseases such as irritable bowel syndrome, ulcerative colitis or bowel cancer. Due to its high affinity for ammonium, clinoptilolite has the **potential to be used as an adjuvant therapy** for these and other indications.

In animals, clinoptilolite treatment has various positive effects such as **improved nitrogen detoxification, reduced mycotoxin load or reduced lead load.** In addition **antioxidant, hemostatic and antidiarrheal** effects have been observed.

#### Effects on oxidative stress and the immune system:

Aerobic organisms continuously produce small amounts of ROS (reactive oxygen species). While the controlled production of ROS is essential for the health of the organism, excessive production of ROS (oxidative stress) causes damage to DNA, proteins and lipids. Oxidative damage is ultimately involved in the pathogenesis of numerous diseases, including obesity, atherosclerosis, heart failure, kidney disease, high blood pressure, neurological diseases and cancer. It is therefore particularly important to keep ROS production and antioxidant processes in balance. The body uses enzymes such as SOD and ROS scavengers such as vitamin C as antioxidant systems.

Interestingly, **clinoptilolite** treatment shows **positive effects on the antioxidant capacitie**s of the organism in different animal models, such as improved SOD activity and reduced lipid peroxidation in the liver, improved antioxidant capacities of the intestinal mucosa, reduced oxidative damage in the cerebral cortex and medulla oblongata, and even improved SOD activity and reduced Aα levels in an Alzheimer's mouse model.

Zeolite treatment also showed **antibacterial and antiviral effects** in various studies, which could be due to immunomodulatory properties. For example, clinoptilolite reduced the number of E. coli and increased the number of health-promoting Lactobacillus acidophilus. *In vitro*, clinoptilolite was shown to have antiviral properties against human adenovirus 5, herpes simplex virus type 1, human enteroviruses coxsackievirus B5 and echovirus 7. In addition, zeolite treatment of patients with immunodeficiencies had positive effects on the number of certain immune cells (B lymphocytes CD19+, T helper cells CD4+, activated T lymphocytes HLA-DR+).

A plausible explanatory model for the immunomodulatory effect of clinoptilolite is the modulation of the body's own defense mechanisms against ROS. In fact, ROS induce cell and tissue damage when inflammation occurs as a mechanism to restore the body's homeostasis. In addition, clinoptilolite interacts with M-cells (microfold cells), which in turn induce an immune response in the Peyer's plaques of the gut-associated lymphoid tissue (GALT).

#### Toxicology:

The European Food Safety Authority (EFSA) evaluated and proved the non-toxicity of zeolite clinoptilolite for animal feed at doses of 10000 mg/kg. According to EFSA, the oral intake of this type of zeolite does **not pose a potential risk for *in vivo*** applications due to its extreme chemical stability.

In a preclinical toxicology study in rodents, in accordance with the requirements of the OECD standards and regulations, the clinoptilolite and its effects associated with increasing exposure time (1 month to 1 year) were evaluated. Despite an increased dose (10 - 25 times higher than the exposure dose for humans), the study showed **no toxicity** in the test animals.

Further studies showed a **protective effect** of clinoptilolite on the **hematocrit and hemoglobin levels** as well as on the **cadmium content in the liver** of pigs. Furthermore, natural clinoptilolite **showed no effects on the reproductive capacity** of female rats and proved to be non-genotoxic in the Ames

bacterial test. In addition, no influence of clinoptilolite on the body mass index or serum chemistry of mice was observed.

Due to the **high affinity of clinoptilolite for lead**, public concerns have been expressed that lead from clinoptilolite materials could penetrate the intestine. However, it has been shown that **the sorption of lead and cadmium (Cd) on natural clinoptilolite is irreversible** or only very slowly reversible. In addition, the adsorption capacity of zeolite for lead is in the pH range of 3 - 11, the leaching of lead from lead-preloaded clinoptilolite mainly occurs at a non-physiological pH value below 1. Results of studies also showed a detoxifying effect of clinoptilolite as well as a **reduction of the Pb content *in vivo.***

In classic detoxification processes, physiologically important electrolytes can be removed from the serum. However, this was not observed in clinoptilolite trials in humans and animals. Long-term intake has also not led to significant changes in physiologically relevant trace elements or vitamins.

In summary, it can be said that the clinoptilolite materials that have been scientifically tested have generally proven to be **safe for *in vivo* applications.** Nevertheless, **each material** has its own physico-chemical properties and **specific biological effects** that cannot easily be transferred to other materials.

### Conclusion

In accordance with the scientific literature, clinoptilolite materials (including activated materials) can be considered **safe for *in vivo* use**. Due to the remarkable ion exchange and adsorption properties of clinoptilolite and the resulting detoxifying effect, clinoptilolite has been shown to be useful in the **removal of harmful substances** from the body. The observed positive systemic effects are at least partly due to the restoration of homeostasis, due to local **detoxification properties in the intestine, antioxidant effects** and **secondary immunomodulatory effects** of clinoptilolite.



## 3.2.2. Test series on the effect on the microbiome [35]

### Introduction and background

Based on evidence from publications stating that the natural zeolite clinoptilolite has a positive influence on the microbiome [36, 37, 38] as well as a gold standard study on leaky gut through oral supplementation with PMA-Zeolite®, an *in vitro* setup was carried out to test the direct influence of PMA-Zeolite® on intestinal bacteria.

### Methods

The tests were carried out with a probiotic and PMA-Zeolite®. The tests were performed in accordance with the anerobic physiological conditions in the gastrointestinal tract and the corresponding incubation time and temperatures at 37° C.

### Results

There were statistically significant changes regarding the influence of the probiotic on growth when dosed according to the packaging instructions.

### Conclusion

Evidence from previously published studies on the positive influence of essential bacterial strains on the human microbiome (especially Lactobacillus and Bifidobacterium) is confirmed by this test arrangement with PMA-Zeolite®. The mechanism of this observed positive effect of PMA-Zeolite® on the growth of the probiotic remains unknown to date. Based on the scientific research, the following hypotheses are proposed:

- The fissured, microporous surface provides physical protection for bacteria. [39]
- The release of physiological cations (e.g. calcium, magnesium, potassium) could also contribute to this, as lactobacilli and bifidobacteria can produce exopolysaccharides (EPS), which are important for creating a suitable growth environment. The production of EPS is related, to the pH value or the availability of minerals (which is provided by the PMA Zeolite®). [25] Further studies are planned to substantiate these initial results.

## 3.2.3. Investigation of the antioxidant activity of PANACEO [40]

### Introduction and background

The aim of the study was to investigate the antioxidant activity and mechanism of action of PMA-Zeolite®.

### Methods

The samples consisted of PMA-Zeolite® packaged in commercially available packaging. The DPPH (1,1- diphenyl-2-picryl-hydrazyl) test, which utilizes the redox reaction of an antioxidant with the stable DPPH radical and thus measures the property as a direct antioxidant, and various emulsion oxidation approaches were used for the test series. These emulsion oxidation approaches imitate biologically important lipid peroxidation processes (e.g. oxidation of lipoproteins, lipid emulsions, meat homogenates) and thus the effect on the formation of free radicals.

### Results

- Lipid peroxidation with AAPH (radical generator): an antioxidant effect is observed with the peroxyl radicals formed from AAPH, which is probably due to the ability of the PMA-Zeolite® to bind cations (the corresponding peroxyl radicals are cationic). One mg PANACEO results in an extension of the lag-phase by about 120 %.
- Lipid peroxidation through Cu catalysis: $Cu^{2}$+ ions can catalytically form radicals from lipid hydroperoxides. As $Cu^{2}$+ is already effective at low concentrations, the quantities used all lead to a roughly equal delay in oxidation by about 100. The cation binding capacity of PMA-Zeolite® is therefore also likely to be decisive here.
- Muscle meat oxidation: this is also delayed by PANACEO by around 50 %. Again, there is no real concentration dependence, which has similar reasons to $Cu^{2}$+ -catalyzed lipid peroxidation.
- DPPH test: this shows that the PMA-Zeolite® does not directly react with the stable radical.

## Conclusion

In summary, PMA-Zeolite-Clinoptilolith® is effective due to its ion exchange capabilities, even at physiologically high ionic strengths and low pH values. PMA-Zeolite® acts as a primary, non-enzymatic antioxidant and reduces the catalytic formation of radicals by binding transition metal ions, both *in vitro* in pure lipid emulsions and in more complex systems. The formation of new free radicals (ROS) can thus be reduced by up to 50 %.

### 3.2.4. Alzheimer's animal model – reduction of oxidative damage [41]

## Introduction and background

The purpose of this study was to investigate the antioxidant and protective properties of PMA-Zeolite® for cell protection (more precisely: protection against oxidative damage in neurodegenerative diseases). This study is also related to the pollutant load of the organism from the environment and the question regarding the protective influence of PMA-Zeolite® on the antioxidant system.

## Methods

After pro-oxidative stimulus (i) *in vitro* cell death and oxidative stress were determined in a neuronal-like cell line. Antioxidant activity and amyloidogenic processing of beta-amyloid were (ii) evaluated *in vivo* after 5-month enrichment of drinking water with PMA-Zeolite® in an animal model (mice).

## Results

The experimental set-ups used in neuronal cells in vitro and in the model organism *in vivo* clearly show the positive effect of the PMA-Zeolite® in neurodegenerative diseases such as Alzheimer's disease. The mitochondrial formation of reactive oxygen species (ROS), which play a key role in the regulation and control of cell survival and death (through interaction with cellular macromolecules and signal transduction pathways) could (i) be reduced *in vitro* by treatment with zeolite. *In vivo* (ii) protection against oxidative damage could be documented through the activation of metalloenzymes (SOD1 and SOD2 = superoxide dismutases as endogenous antioxidant enzymes and effective radical scavengers). In addition, a decrease in amyloid plaques (= incorrectly folded peptides that are deposited between the neurons and tau fibrils - twisted protein fibers - inside brain cells and are characteristic of Alzheimer's disease) was measured in the brain.

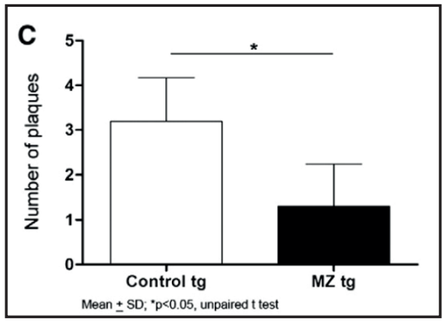


**Figure 14:**
The number of amyloid plaques (incorrectly folded peptides) is significantly reduced in PMA-Zeolite®-treated animals.

## Conclusion

PMA-Zeolite® can support anti-oxidative processes by releasing active minerals and trace elements. On the one hand, the mitochondrial formation of reactive oxygen species (ROS) is reduced and on the other hand, the endogenous antioxidant enzyme superoxide dismutase (SOD), which is an effective radical scavenger, is increased. This increase may be due to the release of minerals (manganese or copper and zinc) by the PMA-Zeolite®. This is because the minerals just mentioned are co-factors in the activation of metalloenzymes such as SOD1 and SOD2. These can protect the organism from oxidative damage. It should also be mentioned that the PMA-Zeolite® achieved significantly better results than conventional natural zeolite clinoptilolite.

The gastrointestinal tract in particular (defined area of action of PMA-Zeolite®), is exposed to a number of relevant pathogenic substances (e.g. heavy metals). Zeolite can counteract this exposure through its selective ion exchange capabilities. For example, heavy metal ions or transition metal ions are exchanged for the free cations ($Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$) stored in the zeolite.

Science confirms the connection between neurological diseases and the gut. This link has been described as the "gut-brain axis". [42] Based on a review and the results described on the use of PMA-Zeolite® in neurodegenerative diseases, PMA-Zeolite® with its antioxidant, anti-inflammatory and gut-protective properties represents a promising approach for use in neurodegenerative diseases. [43]

### 3.2.5. Partial hepatectomy – supporting the liver's ability to regenerate [1]

## Introduction and background

The aim of this study was to demonstrate the improved regenerative capacity of liver cells through the supplementation of zeolite.

## Methods

The substances to be supplemented (PMA-Zeolite®, untreated zeolite clinoptilolite and M.D.) were administered in the complex model organism one week before the surgical procedure in which 70 % of the liver mass was removed. The liver tissue and blood serum were analyzed after supplementation and after the 70 % hepatectomy.

## Results

In addition to the generally significantly better effect of PMA-Zeolite® on liver regeneration compared to untreated zeolite clinoptilolite and M.D., the most significant result from this study is an increase in the antioxidant capacity of the liver cells. This is because a reduction in malondialdehyde (MDA) on the one hand and an increase in reduced glutathione (GSH) on the other were demonstrated.

## Detailed results MDA:

This key biomarker for oxidative stress decreased significantly after supplementation with PMA-Zeolite®. This indicates an immediate reduction in oxidative stress. The MDA plasma level is significantly lower after supplementation with PMA-Zeolite® than with M.D. This also applies to a comparison with untreated zeolite clinoptilolite. PMA-Zeolite® therefore has a significantly better effect compared to untreated zeolite, and even compared to an active ingredient often used as a liver therapeutic agent (M.D.).

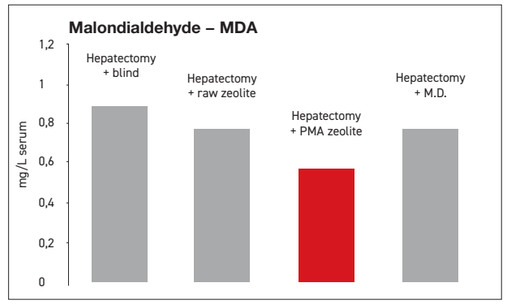


**Figure 15:** Malondialdehyde (MDA) levels in the model organism after partial hepatectomy (70 %) shown in mg/l serum. Four groups can be compared with each other: 1. hepatectomy without further treatment (blind), 2. hepatectomy and supplementation with red zeolite, 3. hepatectomy and supplementation with PMA-Zeolite®, 4. hepatectomy and supplementation with liver therapeutic agent.

## Detailed results GSH:

Treatment with PMA-Zeolite® is observed to increase the plasma level of GSH, one of the body's most important antioxidants. Compared to M.D. and the untreated zeolite clinoptilolite, higher levels were achieved with PMA-Zeolite®. GSH plays a key role in cell protection against reactive oxygen species (ROS), xenobiotics and heavy metals.[44] The regulation of GSH is therefore seen as an important factor in the progression of liver diseases. If too little GSH is available in the liver, this could contribute to hepatocellular cell death.

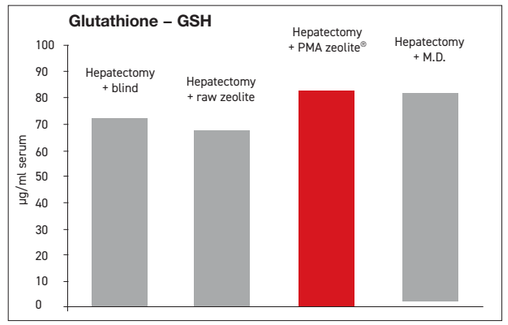


**Figure 16:** Glutathione (GSH) levels in the model organism after partial hepatectomy (70 %) shown in µg/ml serum. Four groups can be compared with each other: 1. hepatectomy without further treatment (blind), 2. hepatectomy and supplementation with red zeolite, 3. hepatectomy and supplementation with PMA-Zeolite®, 4. hepatectomy and supplementation with liver therapeutic agent.

## Conclusion

PMA-Zeolite® cannot only protect the body's own antioxidants (GSH) but can also reduce oxidative damage caused by free radicals (e.g. reduction of lipid peroxidation) due to its microporous structure and cation binding capacity, based on the main physical mechanism of action in the gastrointestinal tract. As a primary, non-enzymatic antioxidant, it reduces the catalytic formation of radicals by transition metal ions, both *in vitro* in pure lipid emulsions and in more complex systems, in order to protect cells from cell death induced by free radicals (ROS).[40] This binding of transition metal ions can explain the antioxidant effect and consequently the decrease in malondialdehyde levels. In the abovementioned study on neuronal cells *in vitro* and in the model organism *in vivo*, it was also found that PMA-Zeolite® can activate metalloenzymes (superoxide dismutases 1 and 2) through the release of trace elements and thus protect against oxidative damage. [41]

The positive effect of PMA-Zeolite® on the liver through its action in the gastrointestinal tract is demonstrated by the gut-liver axis. A publication (2018) [45] shows that a disorder of the intestinal mucosal macrophages is a key factor for disorders of the gut-liver axis. A disturbed intestinal barrier system (leaky gut) on the one hand and dysregulation of intestinal bacteria (microflora) on the other hand play a key role. PMA-Zeolite® has a proven positive influence on the strengthening of the intestinal wall and thus also has an influence on which particles are transported further via the portal vein to the liver, where they are metabolized for energy production or for the biosynthesis of larger structures. A malnutrition (e.g. too much fat or carbohydrates) or medication therefore promote the development of a fatty liver - in this specific case, non-alcoholic fatty liver disease (NAFLD). In addition, dysbiosis of the intestinal flora and impaired intestinal barrier function (so-called leaky gut) can also occur. Unwanted metabolites reach the liver, inflammatory processes are activated, and inflammatory processes are triggered. [46 47]



# Final review

The studies described show that an adequate amount of data on PMA-Zeolite® is available and produced by PANACEO. Its safety, as well as its intended main effect and the main physical mechanism of action in the gastrointestinal tract, as well as a number of indirect systemic secondary effects on the detoxification system and the entire organism, have been proven by preclinical, clinical, placebo-controlled and double-blind studies (i.e. gold standard).

The very good results and interim results documented so far, form a solid basis for future studies focusing on further research into the potential absorption behavior of harmful substances, the effects on the microbiome and intestinal wall functionality as well as further related systemic secondary effects on the organism.
In summary, it should be noted that PANACEO's research activities are based on the latest findings from PMA-Zeolite® research and are carried out on an ongoing basis and in accordance with the highest scientific quality standards.
When designing and implementing our R&D activities, our aim is to be able to guarantee safe and effective products in the interests of our customers. These products are able to make a significant contribution to reducing the burden of negative environmental influences by reducing exposure to harmful substances and strengthening the intestinal barrier function.

## Background information PMA-Zeolite®

It should be explicitly mentioned at this point that there are over 200 different artificial and natural zeolites. The specific natural zeolite clinoptilolite used by PANACEO as the base mineral for its certified medical products consists of a microporous framework structure of aluminum oxide and silicon oxide tetrahedra. The aluminum and silicon atoms are connected to each other by oxygen atoms. This results in a stable structure of uniform pores and/or channels, which in nature contain water that can be removed by heating without changing the zeolite structure. This stability is also evident in acidic and basic pH environments and at temperatures of up to 450° C.

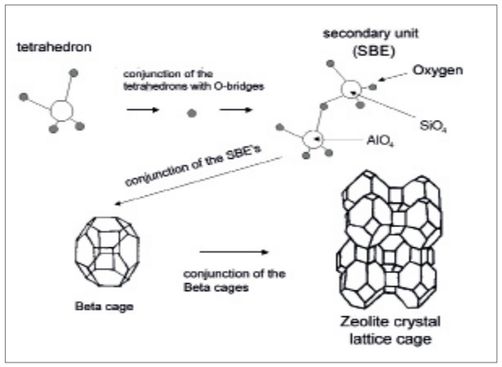


**Figure 17:** Structures of the zeolite crystal lattice of SiO4 and AlO4. The microporous volcanic mineral zeolite is permeated by fine crystal lattice tubules (diameter approx. 0.4 nm). [51]

Precisely because it is a naturally occurring mineral, the quality is decisive for the expected medical success. As with every naturally occurring component, the natural composition of zeolite clinoptilolite also varies depending on the place and location of formation.

This is why PANACEO regularly checks the quality of the deposits and buys the raw material exclusively from companies that have been audited in advance in accordance with the specifications. One of the most important mineralogical quality parameters is a high Si to Al ratio (> 5:1) and a proven clinoptilolite content of > 80 %. In addition, attention is paid to the closest possible occurrence and a gentle mining method in order to keep transportation short and protect the environment. The result is the best possible raw material as the basis for further processing into PMA-Zeolite®.

The PMA process technology is a globally unique process in which the particles of the raw material (zeolite-clinoptilolite) are accelerated against each other under the influence of very high kinetic energies and crush each other. In addition to the desired homogeneous micronization, a modification of the crystal lattice is produced, which leads to a stronger negative surface charge. The now spherical, highly fissured particles have an optimized (because enlarged) outer surface and only an average grain size of around three to five thousandths of a millimetre (5 µm). A calculation of the surface area of the PMA-Zeolite® by the Vienna University of Technology has shown that with a total penetration depth into the pores, 1 gram of the active ingredient produced by PANACEO has an effective surface area of around four thousand square meters. [4]

Numerous studies [1, 2, 3] have shown that the PANACEO micro-activation process can achieve a significantly higher effectiveness compared to the starting material. The effectiveness can be defined by the particle size, the effective surface area and the cation exchange capacity.

Differences in absorption behavior arise primarily in the pH value of the environment. PMA-Zeolite® shows an increased absorption capacity in those areas that are most similar to the human digestive environment.

In summary, it should be noted that the surface enlargement of the micronized PMA-Zeolite® is an important quality parameter and is also responsible for the increased effectiveness (improved absorption capacity).

## Dual mechanism of action in detail

► Leaky gut relief and co-factors

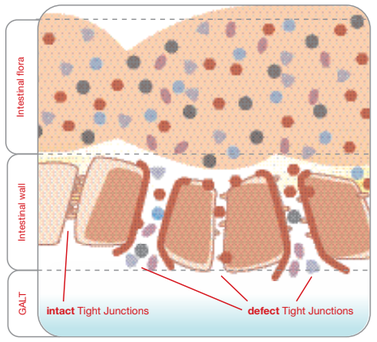


**Figure 10:**
Problem: Permeable intestinal wall

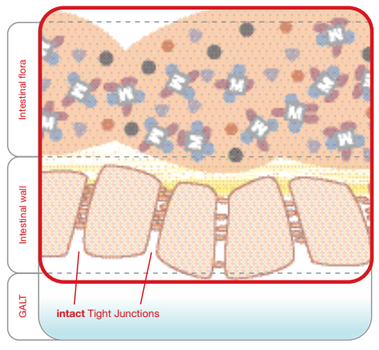


**Figure 11:**
Therapy approach: intestinal wall with PMA-Zeolite®

To fulfill its key role for our health, the healthy gut is equipped with effective control and protection mechanisms on several levels. The three levels of protection work closely together like an interlocking network.

**Protection level 1 - Intestinal flora (intestinal microbiota)**

The intestinal wall is covered with a dense layer of BILLIONS of beneficial intestinal bacteria - our intestinal flora (intestinal microbiota). [52] Their task is, to displace unwanted germs and train our immune system. [53]

**Protection level 2 - Intestinal mucosa (intestinal mucosa)**

The intestinal mucosa is a single-cell layer of epithelial cells that carries a thick layer of mucus on the outside and acts as a selective and effective filter for our health. Together with the intestinal bacteria, the intestinal mucosa forms a mechanical protective barrier when intact.

**Protection level 3 - Gut-associated immune system**

Inside the intestinal wall is a multitude of different immune cells - the gut-associated immune system. The intestine is known to be the largest immune organ, with 80 % of immune cells. The various immune cells either act directly on site or reach their site of action via blood and lymph.

At all levels, a sophisticated system ensures that unwanted substances do not enter the bloodstream and cause damage to the body.

In the PANACEO gold standard study, it was shown that PMA-Zeolite® ensures that the regulatory protein zonulin, a valid marker for measuring the permeability of the intestinal epithelium, could be reduced. If zonulin is elevated, this means that the function of the tight junctions is restricted and the intestinal mucosa no longer closes. The PMA-Zeolite® was able to significantly reduce the level of zonulin ($p < 0.05$), confirming that the filter function of the intestinal wall was restored. [22]

This confirms that the function of the mechanical protective barrier, the intestinal wall with its filter function, can be restored with PMA-Zeolite®. In addition, PMA-Zeolite® improves the effects of probiotics. [35]

► The active principle

The natural cation exchanger PMA-Zeolite®, which is preloaded with minerals and trace elements, is based on absorbing harmful substances in and via the GIT according to a clearly defined lock-and-key principle and, in return, releasing minerals and trace elements due to the osmotic concentration gradient. As a result, the PMA-Zeolite® is not metabolized, but excreted completely and naturally via the stool, loaded with the bound harmful substances. As a result, these substances can no longer damage the intestinal wall as the "guardian" of our immune system. Thus, in accordance with its intended purpose, detoxification is supported (binding of defined pathogenic substances in the GIT).

The cause-and-effect relationship is fundamental to understanding the mechanism of action of the selective cation exchanger PMA-Zeolite®. This can best be illustrated by analogy with a medical product that has a similar purpose, namely the removal of undesirable substances. In hemodialysis, too, the cleansing or detoxification or the supply of desired substances via the blood leads to protection of the organism and its organs and thus prevents secondary diseases. The same basic principle is also used with zeolite. While the ion exchange in hemodialysis takes place via osmosis, the ion exchange in zeolite takes place due to a defined electromagnetic or static interaction between the zeolite crystal lattice structure (negatively charged) and the cations to be absorbed (positively charged).

The ion exchange of cations takes place on the basis of the given selectivity of the natural mineral zeolite-clinoptilolite [54], which is defined by a specific sorption series of certain elements. In addition, the molecular sieve function of the natural zeolite clinoptilolite should also be mentioned, which defines a molecular selection via the pore size of only approx. 0.4 nm of the cavity system. It is important to understand that natural zeolite clinoptilolites have a negative framework charge, which is "balanced" by cations that occur in the channel systems. The cations are minerals such as sodium, potassium, calcium or magnesium as well as trace elements such as zinc, manganese or silicon, which often occur in dissolved form and are therefore relatively easily accessible and exchangeable. Through the defined sorption series, defined pollutants are absorbed via ion exchange and physiologically important minerals and trace elements are released in return.

The sorption series of the natural zeolite clinoptilolite, which forms the base mineral of PMA-Zeolite®, contains caesium > ammonium > lead, starting with the highest affinity. In addition, the gastrointestinal model shows that the heavy metals arsenic, cadmium, chromium and nickel are also bound by PMA-Zeolite® in the gastrointestinal tract.

Based on the high specificity of the PMA-Zeolite®, interactions with orally ingested medications are easy to assess. Interactions are very unlikely due to the molecular size and the necessary charge (cations). To minimize the risk, PANACEO recommends in the safety instructions that the simultaneous intake of PMA Zeolite®, with medication should be discussed with a doctor. Doctors who have already been working with PMA-Zeolite® for years recommend keeping a time interval of one hour between the medication and PMA-Zeolite® (before the medication, as this is absorbed while the PMA-Zeolite® remains in the GIT).

# References


[1] **Pavelič K. et al. (2014 b)**.
Application of natural zeolites on hepatectomized rats could support regeneration of the liver. University of Rijeka. Unpublished.

[2] **Pavelič K. (2012).**
Double activated clinoptilolite effect on cholesterol level in rats. University of Rijeka, Croatia. Unpublished.

[3] **Pavelič Kraljevič S. et al. (2017).**
Novel, oxygenated clinoptilolite material efficiently removes aluminium from aluminium chloride-intoxicated rats in vivo. Microporous and Mesoporous Materials 249 (2017) 146-156.

[4] **Taschner R. (2015).**
Berechnung der zum Zwecke eines Ionenaustausches „effektiven" Oberfläche des von der Firma PANACEO hergestellten Wirkstoffes, Technische Universität Wien. Unpublished.

[5] **DGMIM e.V. (Deutsche Gesellschaft für Mukosale Immunologie und Mikrobiom e.V.) (2019)**.
Internet-Zugriff http://www.dgmim.de/fileadmin/CONTENT/darmbarriere_druck.pdf [04.11.2019].

[6] **Weltgesundheitsorganisation, WHO (2015).**
Fact-Sheet: Bestandsaufnahme der Fortschritte im Bereich Umwelt und Gesundheit in der Europäischen Region.

[7] **Flowers, J. et al. (2009).**
Clinical evidence supporting the use of an activated clinoptiolite suspension as an agent to increase urinary excretion of toxic heavy metals. Nutrition and Dietary Supplements; I: 11-18.

[8] **Joint WHO/Convention Task Force on the Health Aspects of Air Pollution. (2007).**
Health risks of heavy metals from long-range transboundary air pollution.

[9] **RASFF-Portal (2019).**
Internet-Zugriff https://webgate.ec.europa.eu/rasff-window/portal/?event= notificationsList&StartRow=1 [04.11.2019].

[10] **Schriebl-Rümmele M. (2014).**
Zeitbombe Umwelt-Gifte – Wie ein Naturmineral vor Nahrungsmittel- und Umwelt-Giften schützt.

[11] **Khaw, K.T. et al. (2008).**
Combined Impact of Health Behaviours and Mortality in Men and Women: The EPIC-Norfolk Prospective Population Study. PLoS Medicine5 (1) e12. doi:10.1371/journal. pmed.0050012.

[12] **Gecse K. et al. (2012).**
Leaky gut in patients with diarrhea-predominant irritable bowel syndrome and inactive ulcerative colitis. Digestion. 2012;85(1):40-6. doi: 10.1159/000333083. Epub 2011 Dec 14.

[13] **Chang J. et al. (2017).**
Impaired Intestinal Permeability Contributes to Ongoing Bowel Symptoms in Patients With Inflammatory Bowel Disease and Mucosal Healing. Gastroenterology. 2017 Jun 7. pii:S0016-5085(17)35731-1.doi:10.1053/j.gastro.2017.05. 056.

[14] **Mansueto P. et al. (2015).**
Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity. World J Gastroenterol 2015 June 21; 21(23): 7089-7109.

[15] **Leccioli V. et al. (2017).**
A New Proposal for the Pathogenic Mechanism of Non-Coeliac/Non-Allergic Gluten/Wheat Sensitivity: Piecing Together the Puzzle of Recent Scientific Evidence. Nutrients. 2017 Nov 2;9(11). pii: E1203. doi: 10.3390/nu9111203.

[16] **Mu Q. et al. (2017).**
Leaky Gut As a Danger Signal for Autoimmune Diseases. Front Immunol. 2017 May 23;8:598. doi: 10.3389/fimmu.2017.00598. eCollection 2017.

[17] **Nalle S.C. und Turner JR, (2015).**
Intestinal barrier loss as a critical pathogenic link between inflammatory bowel disease and graft-versus-host disease. Mucosal Immunol. 2015 Jul;8(4):720-30. doi: 10.1038/mi.2015.40. Epub 2015 May 6.

[18] **Morris G. et al. (2016).**
The Role of Microbiota and Intestinal Permeability in the Pathophysiology of Autoimmune and Neuroimmune Processes with an Emphasis on Inflammatory Bowel Disease Type 1 Diabetes and Chronic Fatigue Syndrome.

[19] **Saltzman E.T. et al. (2018).**
Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Front Microbiol. 2018 Jan 30;9:61. doi: 10.3389/fmicb.2018.00061. eCollection 2018.

[20] **Pietrzak D. et al. (2017).**
Digestive system in psoriasis: an update. Arch Dermatol Res. 2017 Nov;309(9):679-693. doi: 10.1007/s00403-017-1775-7. Epub 2017 Sep 13.

[21] **Craig J.M. (2016).**
Atopic dermatitis and the intestinal microbiota in humans and dogs. Vet Med Sci. 2016 Feb 23;2(2):95-105. doi: 10.1002/vms3.24. eCollection 2016 May. Vet Med Sci. 2016 Feb 23;2(2):95-105. doi: 10.1002/vms3.24. eCollection 2016 May.

[22] **Lamprecht M. et al. (2015).**
Effects of zeolite supplementation on parameters of intestinal barrier integrity, inflammation, redox-biology and performance in aerobically trained subjects. Journal of the International Society of Sports Nutrition 2015, 12:40 doi:10.1186/s12970-015-0101-z.

[23] **Pavelič Kraljevič S. et al. (2014 a).**
Heavy metal removal from solution by different zeolite materials in artificial stomach and gut models. Unpublished.

[24] **Pavelič Kraljevic, S. et al. (2017).**
Evaluation of ammonia absorption on clinoptilolite materials. Unpublished.

[25] **Pavelič Kraljevic S. et al (2018).**
Critical Review on Zeolite Clinoptilolite Safety and Medical Applications in vivo. Frontiers in Pharmacology 2018;9:1350.

[26] **MVZ Institut für Mikroökologie (2019).**
Internet-Zugriff:http://www.mikrooek.de/fuer-aerzte-und-therapeuten/unsere-diagnostik/unklare-abdominalbeschwerden/zonulin/ [04.11.2019].

[27] **Schulz N .(2007).**
Persönliche Kommunikation, Praxisbericht. Unpublished.

[28] **EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2010).**
Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) claiming biotransformation of xenobiotic substances (ID 1378, 2388, 2401, 3900, 3942, 4039, 4510, 4513, 4544, 4628, 4639), "elimination", "cleansing" and "purification" (ID 1347, 4024, 4442, 4457), elimination of heavy metals (ID 1887, 3156), and maintenance of normal bowel function (ID 4039) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1733. [20 pp.]. doi:10.2903/j.efsa.2010.1733. Available online: www.efsa.europa.eu/efsajournal.htm.

[29] **PANACEO et al. (2014).**
Exzerpt: Österreichweite Pilotstudie zur natürlichen Senkung erhöhter Leberwerte mit Zeolith. Unpublished.

[30] **Weber D. (2012).**
Zeolith bei der Therapie von Essstörungen: Einfluss auf den BMI bzw. Blutparameter.
Kurheim Paracelsus, Warmbad-Villach.

[31] **Pavelič S et al. (2014 f).**
Removal of organochlorine and organophosporus pesticides from solution by different zeolite materials. Unpublished.

[32] **Thoma W. und Gunzer C. (2006).**
Clinical Observation - The antioxidative effect of activated volcano mineral zeolite to the oxidative system.
Privatklinik Villach. Unpublished.

[33] **Knapitsch et al. (2004).**
Sportmedizinische und Sportwissenschaftliche Ordination, Klagenfurt. Die Wirkung von PANACEO Sport auf die Laktatwerte während der körperlichen Anstrengung beim Menschen mit Hilfe einer randomisierten, placebo-kontrollierten Doppelblindstudie.

[34] **Bachl, N (2011).**
Leitung Zentrum für Sportwissenschaft und Universitätssport. Beurteilung der Ergebnisse der randomisierten Doppelblindstudie mit PANACEO Sport.

[35] **Kraljevič Pavelič S. et al. (2019).**
In vitro set-up for the microbiota cultivation and preliminary effects of the PMA-zeolite® on the growth of microorganism mixture Omnibiotic. Unpublished.

[36] **Wu, Q. et al. (2013).**
'Effects of clinoptilolite and modified clinoptilolite on the growth performance, intestinal microflora, and gut parameters of broilers', Poultry Science, 92, pp. 684–692. doi: 10.3382/ps.2012-02308.

[37] **Subramaniam MD und Kim ICH (2015).**
`Clays as dietary supplements for swine: A review`, J Anim Sci Biotechnol. 2015; 6(1): 38. doi: 10.1186/s40104-015-0037-9.

[38] **Prasai TP et al. (2016).**
Biochar, Bentonite and Zeolite Supplemented Feeding of Layer Chickens Alters Intestinal Microbiota and Reduces Campylobacter Load. PLoS ONE 11(4): e0154061. doi:10.1371/journal.

[39] **Azad Mohammad Hassanzadeh et al. (2017).**
Immobilization and microencapsulation of Lactobacillus caseii and Lactobacillus plantarum using zeolite base and evaluating their viability in gastroesophageal-intestine simulated condition. Ars Pharm. 2017; 58(4): 163-170).

[40] **Abuja, P.M. (2006).**
An investigation of the antioxidant activities of PANACEO, TU Graz, Institut für Biophysik und Röntgenstrukturforschung. Unpublished.

[41] **Montinaro M et al. (2013).**
Dietary zeolite supplementation reduces oxidative damage and plaque generation in the brain of an Alzheimer's disease mouse model. 17-19.

[42] **Kaelberer, M.M. et al. (2018).**
A gut-brain neural circuit for nutrient sensory transduction. Science 2018, 361, eaat5236.

[43] **Mastinu A. et al. (2019).**
Zeolite Clinoptilolite: Therapeutic Virtues of an Ancient Mineral; Molecules2019,24, 1517; doi:10.3390/molecules2408151.



[44] **Singhal RK et al. (1987).**
Glutathione, a first line of defense against cadmium toxicity. FASEB J 1, 220-223.

[45] **Saltzman, ET et al. (2018).**
Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Frontiers in Microbiology. January 2018 | Volume 9 | Article 61.

[46] **Wiernsperger, N et al. (2013).**
Hepatic function and the cardiometabolic syndrome. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2013:6 379–388.

[47] **Miele, L. et al. (2009).**
Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology (Baltimore, Md.), 49(6), pp. 1877–1887. doi: 10.1002/hep.22848.

[48] **Radermacher-Reuter, G. und Martin, L. (2015).**
Leaky Gut – Testverfahren zum Nachweis einer gestörten intestinalen Permeabilität. Fachinformation 0090. Ganzimmun Diagnostics GmbH.

[49] **Halbfurter, M. (2014).**
Leaky Gut - Eine wissenschaftliche Literarturanalyse. Wien. doi: 10.7748/ns2011.08.25.51.30.p6185.

[50] **Sudowe, S.P.D. (2015).**
Endotoxinämie - LPS im Serum als Marker für Silent Inflammation', GANZIMMUN Diagnostics AG, 0086(002), p. 12.

[51] **Hecht K. et al. (2008).**
Naturmineralien Regulation Gesundheit. IFOGÖT-Reihe. Schibri-Verlag Berlin-Milow.

[52] **Moreau, M.C. and Gaboriau-Routhiau, V. (2001).**
Influence of resident intestinal microflora on the development and functions of the gut-associated lymphoid tissue. Microbial Ecology in Health and Disease, 13(2), pp. 65–86. doi: 10.1080/089106001300136138.

[53] **Helander, H.F. and Fändriks, L. (2014).**
Surface area of the digestive tract-revisited, Scandinavian Journal of Gastroenterology, 49(6), pp. 681–689. doi: 10.3109/00365521.2014.898326.

[54] **Colella C. et al. (2014).**
The IZA Handbook of Natural Zeolites: A tool of knowledge on the most important family of porous minerals. Microporous and Mesoporous Materials. 189, 4-10.

[55] **Fasano A. (2012).**
Leaky Gut and Autoimmune Diseases, Clinic Rev Allerg Immunol . DOI 10.1007/s12016-011-8291-x.

[56] **Fortschrittsbericht Umsetzung des Prozesses Umwelt und Gesundheit in Europa WHO (2022).**
EUR/RC72/17(C).

[57] **Petkov V. et al. (2021)**
PMA-zeolite® can modulate inflammation associated markers in irritable bowel disease - an explorative randomized, double blinded, controlled pilot trial. Neuro Endocrinol Lett. 2021 Mar;42(1):1-12.

[58] **Mosgoeller, W. et al. (2024)** 'PMA-zeolite® (Clinoptilolite) in the Management of Irritable Bowel Syndrome – a Non-Interventional Study', Zeitschrift für Gastroenterologie [Preprint]. https://doi.org/10.1055/A-2223-3963.

[59] **Kraljević Pavelić S. et al. (2020)** Treatment of osteoporosis with a modified zeolite shows beneficial effects in an osteoporotic rat model and a human clinical trial. Exp Biol Med (Maywood). 2021 Mar;246(5):529-537. doi: 10.1177/1535370220968752. Epub 2020 Nov 12.

[60] **Kraljević Pavelić S. et al. (2022)**
Clinical Parameters in Osteoporosis Patients Supplemented With PMA-Zeolite® at the End of 5-Year Double-Blinded Clinical Trial. Front Med (Lausanne). 2022 Jun 27;9:870962. doi: 10.3389/fmed.2022.870962.

[61] **Vitale M.G. et al. (2020)**
ZeOxaNMulti Trial: A Randomized, Double-Blinded, Placebo-Controlled Trial of Oral PMA-Zeolite® to Prevent Chemotherapy-Induced Side Effects, in Particular, Peripheral Neuropathy. Molecules. 2020 May 13;25(10):2297. doi: 10.3390/molecules25102297.

[62] **Vitale M.G. et al. (2022)**
Survival analyses of the ZeOxaNMulti trial: Follow-up randomized, double-blinded, placebo-controlled trial of oral PMA-zeolite® to prevent chemotherapy-induced side effects, especially peripheral neuropathy. Front Pharmacol. 2022 Nov 8;13:874028. doi: 10.3389/fphar.2022.874028.

[63] **Kraljević Pavelić et al. (2022)**
Clinical Evaluation of a Defined Zeolite-Clinoptilolite Supplementation Effect on the Selected Blood Parameters of Patients. Front Med (Lausanne). 2022 May 27;9:851782. doi: 10.3389/fmed.2022.851782.

[64] **Zechner et al. (2021)**
Plausibilisierungsstudie Sicherheit (Nebenwirkungen) und Wirksamkeit von PMA-Zeolith® bei Patient:innen mit Alkoholproblemen und abnormalen Leberparametern (unpublished).

[65] **Kraljević Pavelić et al. (2018)**
Critical Review on Zeolite Clinoptilolite Safety and Medical Applications in vivo. Front Pharmacol. 2018 Nov 27;9:1350. doi: 10.3389/fphar.2018.01350.



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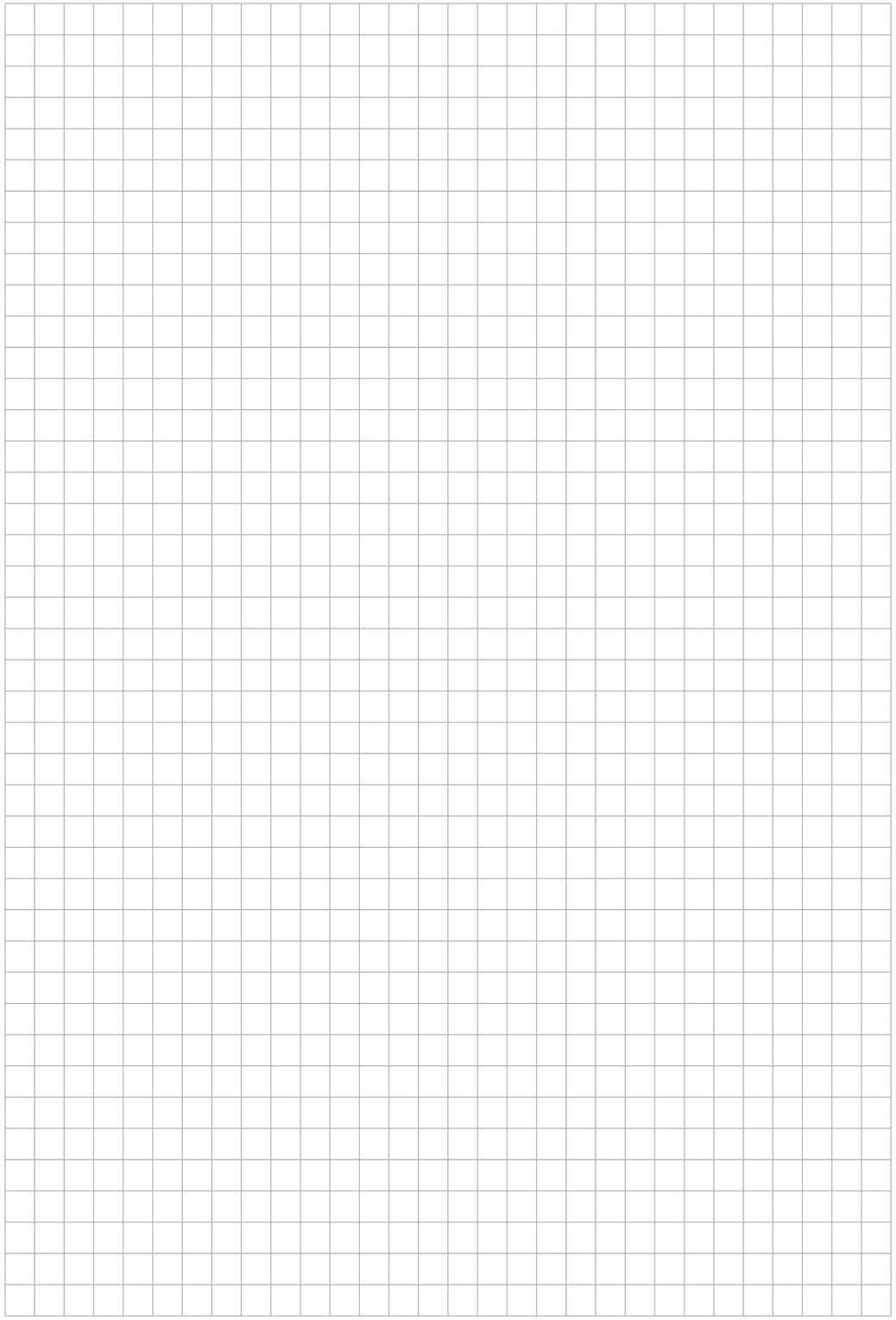



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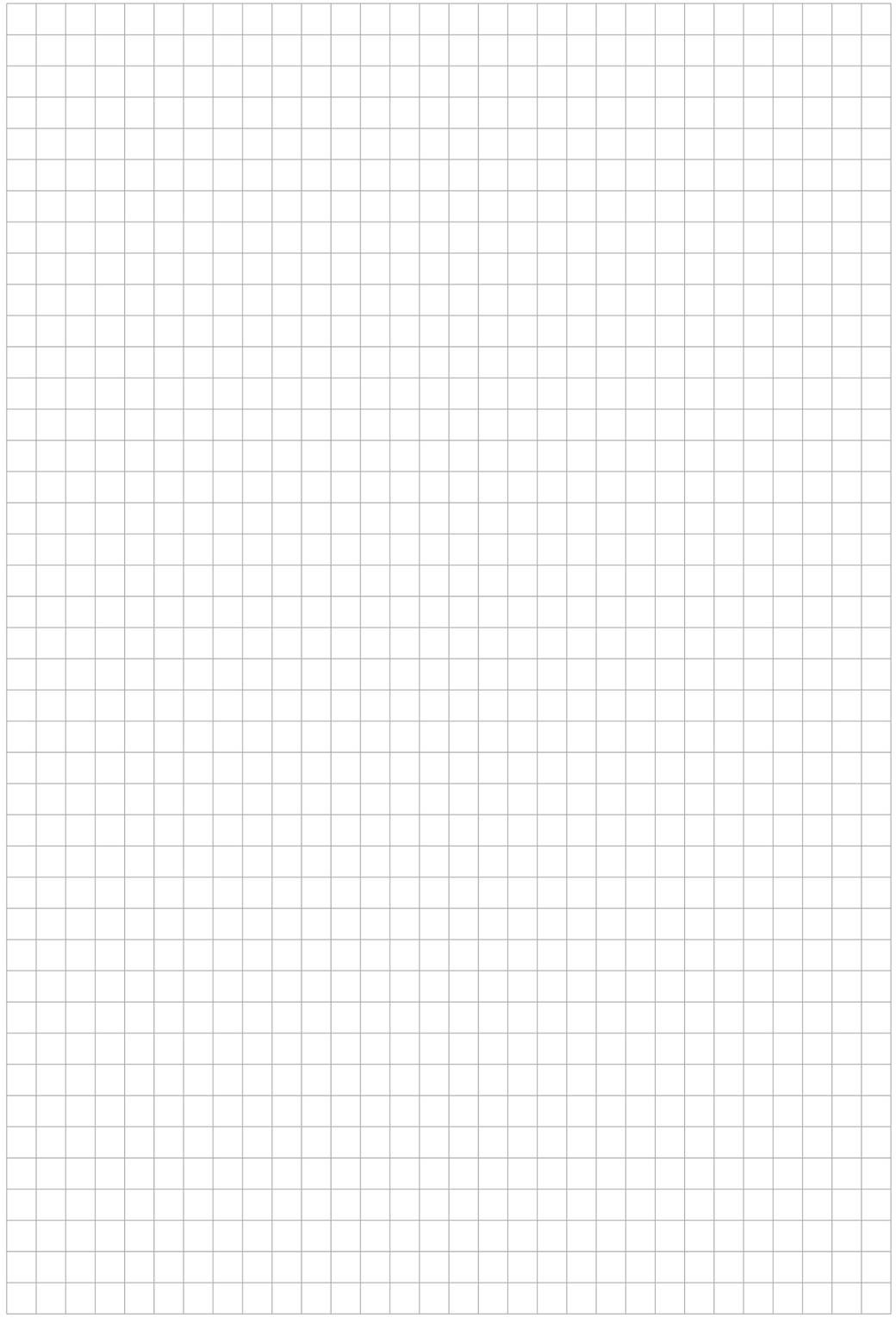

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