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► **To cite this version:**

Aleksandar Nikolov, Lili Dobрева, Svetla Danova, Jeny Miteva-Staleva, Ekaterina Krumova, et al..
Natural and Modified Zeolite Clinoptilolite with Antimicrobial Properties: a Review. *Acta Microbiologica Bulgarica* , 2023, 39 (2), pp.147-161. hal-04157228

HAL Id: hal-04157228

<https://hal.science/hal-04157228v1>

Submitted on 19 Jul 2023

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Review

Natural and Modified Zeolite Clinoptilolite with Antimicrobial Properties: a Review

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Abstract

The present review summarizes research on the antimicrobial properties of modified natural zeolite clinoptilolite. The modification of the clinoptilolite is based on its ion exchange features with silver, copper, zinc, or other ions in order to obtain antimicrobial properties. The review includes recent data on pretreatment and preconditioning to increase the effectiveness of ion exchange procedures and obtain a functionalized zeolite. The review covers antibacterial, antifungal, antiviral properties on natural zeolite clinoptilolite.

Keywords: natural zeolite, clinoptilolite, antimicrobial, antibacterial, antifungal, antiviral.

Резюме

Настоящата обзорна статия обобщава изследванията върху антимикробните свойства на природен и модифициран зеолит - тип клиноптилолит. Модифицирането на клиноптилолита се базира на йонообмен със сребърни, медни, цинкови или други йони, като получената модифицирана форма притежава антимикробни свойства. Обзорът включва информация за предварителното третиране на зеолита с цел повишаване на ефективността на йонообменните процедури и получаване на функционализиран зеолит. Представени са данни за антибактериалните, антифунгалните и антивирусни свойства на природен зеолит и негови модификации.

Introduction

Antimicrobial materials have quickly become a key tool in the global strategy to combat pathogens. The development and progress in the fields of materials science, biotechnology, and microbiology bring research on modern advanced materials with antimicrobial properties (Cloutier *et al.*, 2015). Nowadays, the issue of the continuing growth of microbial resistance to antibiotics and antimicrobial agents (Davies *et al.*, 2013) and the elevation of microbial-related diseases necessitate the needs of improvement of antimicrobial agents or the development of new products that can replace the existing non-effective commercial antimicrobial agents (So *et al.*, 2010). In recent decades, a wide range of different antimicrobial agents has been used successfully, such as antibiotics (Zilberman and Elsner, 2008; Campoccia *et al.*, 2013)

antimicrobial peptides (Kazemzadeh-Narbat *et al.*, 2013; Glinel *et al.*, 2012), individual elements (Lemire *et al.*, 2013; Cloutier *et al.*, 2015), enzymes (Eby *et al.*, 2009; Zhou *et al.*, 2014; Milenkovic *et al.*, 2015), organic cations compounds (del Olmo *et al.*, 2020; Rusew *et al.*, 2020; Xin *et al.*, 2020), organic non-cationic compounds (Baveja *et al.*, 2004; Kazemzadeh-Narbat *et al.*, 2013) and other inorganic compounds (Rtimi *et al.*, 2013; Michl *et al.*, 2015; Storm *et al.*, 2015). Many antimicrobial materials cannot support disinfection properties in the long term *per se*. They provide a rapid peak release of the antimicrobial agent at an early age, resulting in the loss of antimicrobial activity over time. To ensure an antimicrobial effect over time, microporous materials, like zeolites, could be used, where the mechanism of release of the biocide agent is

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governed by the process of ion exchange, which is considerably slower over time.

Zeolite minerals are inorganic crystalline, hydrated aluminosilicates characterized by a unique structure based on an infinitely extended three-dimensional framework composed of alumina and silica tetrahedra connected via oxygen atoms (Bish and Ming, 2018). The substitution of Al^{3+} for Si^{4+} results in a negatively charged aluminosilicate lattice, where alkali and alkaline earth cations (most often Ca^{2+} , Na^+ , K^+) maintain electroneutrality (Baerlocher *et al.*, 2007). Cations are bonded with the zeolite framework by electrostatic forces and occur in the open channels of the zeolites, which are potentially exchangeable through diffusion in a medium containing another cation (Yeasmin *et al.*, 2016). Under appropriate conditions, these cations are potentially exchangeable with Ag^+ , Cu^+ , Zn^{2+} , NH_4^+ , Cs^+ , Sr^+ , Ba^{2+} , Li^+ or other cations (van Koningsveld, 2007). Thus, through ion exchange procedures, a modified form of natural zeolites with specific properties could be obtained (Provdar and Baghdachi, 2007). The ion exchange process often includes a pretreatment step to increase the efficiency of the procedure. Cation selectivity and ion exchange capacity are varied for different zeolites. There are over 40 natural and more than 180 synthetic zeolite mineral species. Synthetic zeolites underwent rapid development due to their higher efficiency. However, natural zeolites offer sufficient effectiveness and no cost for synthesis. Among 40 natural zeolites, only seven (clinoptilolite, chabazite, mordenite, erionite, ferrierite, analcime, and phillipsite) are being commercially exploited (Szerement *et al.*, 2014). The worldwide mine production of natural zeolite is estimated to be 1.1 megatons in 2020 (Summaries, 2021). Most of the large mining countries typically utilize natural zeolite in low-value, high-volume applications such as construction and agriculture. The top 10 countries mining natural zeolites represent 98.7% of the total worldwide mined production, and they are as follows in descending order – China, Republic of Korea, Indonesia, Slovakia, New Zealand, USA, Turkey, Cuba, Russia, and Hungary, according to estimated data for 2020 (Summaries, 2021). The application of zeolites in bio-medical and veterinary fields started in the 1960s, with the use of clinoptilolite and mordenite-rich tuffs as active additions to animal diets in Japan (Minato, 1968). Since then, the applications of natural zeolites have multiplied greatly and expanded to different medical applications (Colela, 2010). Antimicrobial materials based

on raw or modified natural zeolites are considered to be prospective and high-value products involved in the prevention of the spread of pathogens and epidemics/pandemics threatening the lives of the population and national security.

The paper reviews the research on antimicrobial (antibacterial, antifungal, antiviral) properties of raw and modified natural zeolites. The paper summarizes the approaches and procedures for the functionalization or modification of natural zeolites in order to obtain antimicrobial materials.

Preconditioning and ion exchange of natural zeolites

The ion exchange performance of natural zeolites can be improved by different pre-treatment procedures (Mamba *et al.*, 2010; Yeasmin *et al.*, 2016). The most prominent pre-treatment procedures include thermal activation, tribology activation, chemical conditioning/treatment, or a combination of them. The chemical conditioning procedure is based on treating the zeolite with a chemical solution in order to enhance the following effective ion exchange. One of the approaches is the replacement of exchangeable cations from zeolite with a particular cation to achieve a near homoionic form. The conditioned zeolites have improved effective ion-exchange capability by making the exchangeable ions presented within the zeolite more accessible (Panayotova *et al.*, 2018). Many authors revealed that potassium and calcium ions stronger hold onto clinoptilolite than sodium (Ćurković *et al.*, 1997; Inglezakis *et al.*, 2001; Pabalan and Bertetti, 2001). Therefore, the most used conditioning of natural zeolites is the sodium homoionic form. It has been confirmed by recent studies that the sodium ions located in the structure of zeolites are the easiest to exchange with other metallic ions (Kaali and Czél, 2013). Cations interact with water molecules to form hydration spheres. In general, the hydrated radius is inversely proportional to the cation radius, and divalent cations usually have a higher hydrated radius than monovalent cations (Palmer and Gunter, 2001). This may explain why small divalent alkaline-earth cations, Ca^{2+} and Mg^{2+} , cannot move easily out of the channels due to their considerably higher hydrated radii. However, the sodium form of clinoptilolite showed considerable selectivity towards silver, whereas it was unselective for zinc and copper ions except in low-concentration regions where a modest selectivity of the clinoptilolite was observed (Top and Ülkü, 2004). To obtain sodium form, usually, the natural zeolite is treated one or several times with a water solu-

tion of sodium salts such as NaCl, NaSO₄, NaNO₃. Temperature and sodium concentration improve the sodium ion exchange in the zeolite (Ćurković *et al.*, 1997). Sodium hydroxides were sometimes added to raise the solution pH to 11 to accelerate the process (Yeasmin *et al.*, 2016). Excess sodium cations and nitrate, sulfate, or chloride ions after conditioning were removed by washing with distilled water.

Another effective form of zeolite is the so-called H-form. The procedure is more complex and energy consuming, including two steps: first, ammonium form is obtained by treating the zeolite with an ammonium water solution (most used as nitrate, sulfate, or chloride form), followed by thermal treatment at about 350-500°C to expel the ammonium ions and obtain near hydrogen form or H-form. On the other hand, near hydrogen form could also be obtained with acid treatment of the natural zeolite with diluted HCl, H₂SO₄, or HNO₃ acid solutions. The presented cation in the raw zeolite was hydrolyzed to H⁺. The main drawback of acid treatment is the dealumination of the zeolite, which significantly reduces its theoretical ion exchange capacity.

The thermal pretreatment of the zeolite has been applied to increase the effectiveness of the ion exchange procedure. The structure of the clinoptilolite was completely destructed (amorphized) at a temperature of 900°C (Nikolov *et al.*, 2020). The thermal stability of zeolite is related to the type and chemical composition of the zeolite, where potassium-rich clinoptilolite showed higher thermal stability (Dimowa *et al.*, 2013). Thermal pretreatment up to 400°C dehydrates the zeolite water and empties the meso- and macropores and generally improves the effectiveness of the following ion-exchange process.

The triboactivation also plays an important role by decreasing the particle size and thus increasing the specific surface of the powdered zeolitic material. Acceleration of processes is observed due to the accumulation of structural defects in combination with a highly developed reaction surface (Petkova *et al.*, 2011). Triboactivation is performed by milling in different types of mills such as ball mill, jet mill, planetary mill, vibrational mill, etc. The milling could be dry or wet in the case of using liquid media such as water, ethanol, or others. The use of chemical additives improves the efficiency of both wet and dry milling. Additives in dry grinding cover the particles and prevent agglomeration. In wet grinding systems, their main influence is on the slurry rheology (Fuerstenau, 1995). Generally,

wet grinding is more effective than dry milling but produces a waste solution. However, the triboactivation complicates the ion exchange procedure - the filtration and washing step, hence usually triboactivation is performed as the last stage of product preparation in order to increase the specific surface and activity.

The pretreatment procedures are important in terms of increasing the effectiveness of ion exchange and obtaining a functionalized zeolite such as Ag-, Cu-, Zn-, or other forms of zeolites. The complete procedure is based not only on the desired end-effect and properties but also on economic considerations such as saving valuable solutions (such as silver nitrate), avoiding several solution treatments, reducing waste solutions, etc. The modified zeolites prepared using the above-mentioned methods showed improved ion exchange properties, which could be used to obtain antimicrobial forms of zeolites.

Antimicrobial activity of natural and modified zeolite clinoptilolite

Antagonistic activity against different types of pathogens - bacteria, fungi, and viruses is discussed.

Antibacterial properties

Alternative antibacterial agents are needed in the age of increasing antibiotic resistance. Inorganic agents, such as transition metal ions (Ag⁺, Zn²⁺, Cu²⁺, Fe²⁺) possess broad-spectrum antimicrobial activity and have long-lasting active periods. They are safe for humans and minimally toxic (Rassouli *et al.*, 2018). They have been used in combination with zeolites to control their release and antimicrobial properties. In contrast, pure natural zeolite has been deemed much less active or inactive (Rivera-Garza *et al.*, 2000; Akhigbe *et al.*, 2014; Milenković *et al.*, 2017; Sutianingsih and Kurniawan, 2022). The negative charge of pure zeolite cannot modify the bacterial cell wall, since both repel each other due to their negative charges. The individual cations supported by natural zeolites with antibacterial activity are discussed below:

Ag-zeolite

Numerous studies investigate the antibacterial activity of silver incorporated in zeolite. Silver-modified zeolite is widely applied as an antimicrobial agent since it has been determined to possess wide antibacterial activity due to the silver ion being released from the zeolite. The antibacterial activity of silver zeolites has been determined toward both Gram (+) and Gram (-) (Dutta and Wang,

2019; Nikolov *et al.*, 2023). When released from zeolite, it provides a long-term effect (Wattanawong and Aht-Ong, 2021). It's been determined that the antibacterial activity of silver on zeolite is dose/concentration dependent as well as time and type of microorganism dependent (De la Rosa-Gomez *et al.*, 2008; Jiraroj *et al.*, 2014). The antibacterial approaches using natural zeolites are mainly focused on silver release modifications obtained by different procedures resulting in modified zeolites containing silver ions, metal silver nanoparticles, or silver nanocomposites.

Clinoptilolite containing Ag⁺ ions. The bactericide mechanism of the released silver ion from zeolite is considered to be due to the disruption of the bacterial cell wall and membrane (Cheun, 1996; Matsamura, 2003). In addition, inhibition of DNA replication and enzymes for ATP production is a supposed mechanism. Moreover, the generation of reactive oxygen species, which are produced possibly through the inhibition of respiratory enzymes by silver ions and attack the cell itself (Kourai *et al.*, 1994; Inoue and Kanzaki, 1997; Miyoshi *et al.*, 1998).

Hrenovic *et al.* (2013) determined the antibacterial activity of modified natural clinoptilolite against the hospital-causing infectious bacteria *Acinetobacter baumannii*. The effect was not dependent on the type of natural zeolite used as support material, but rather on the cations loaded onto natural zeolite. Silver ions exchanged zeolite exhibited superior inhibitory activity toward the growth of *Pseudomonas aeruginosa* and *Escherichia coli* in comparison with zinc and copper exchanged Na-zeolite (Top and Ülküm, 2004). Silver clinoptilolite showed considerable superiority over zinc clinoptilolite and copper clinoptilolite in terms of antibacterial activity due to the selectivity sequence of clinoptilolite (Ag⁺ > Na⁺ > Zn²⁺ > Cu²⁺) (Top and Ülküm, 2004).

According to Dimowa *et al.* (2014) out of modified Ag-, Cs-, Zn-, Cd-, Ba, only Ag- and Cd-clinoptilolite exchanged forms were able to inhibit the growth of *E. coli* BL21. The antibacterial activity of Ag and Cd clinoptilolite forms was achieved in concentration below 10 µg ml⁻¹ (corresponding to ~ 0.093 and ~ 0.048 µg ml⁻¹ for Ag and Cd-clinoptilolite due to the release of the Ag and Cd cations (Dimowa *et al.*, 2014).

The activity of natural zeolite (NZ) containing 2.03 wt% of Cu²⁺ (CuNZ), 5.07 wt% of Ag⁺ (AgNZ) showed bactericidal activity toward *A. baumannii* belonging to European clone I and II,

with clone II revealing more sensitivity - minimal bactericidal concentration – 125 (for CuNZ) and 31.2mg L⁻¹(AgNZ), while for clone I respectively 250 mg L⁻¹ for both CuNZ and AgNZ (Hrenović *et al.*, 2013). Clinoptilolite modified with silver ion and followed by phosphoric acid treatment revealed *E. coli* ATCC 25922 antibacterial activity, achieving a gradual silver release from the tested materials (Karel *et al.*, 2015).

Zeolite has wide applications in water treatment. A study by Akhigbe *et al.* (2014) determined the highest reduction capability of silver-modified clinoptilolite toward *E. coli* NCTC 9001 in 30 min of contact time in deionized water, but no activity for non-modified zeolite. Antibacterial activity was not inhibited by the presence of metal ions such as (Pb²⁺, Cd²⁺, and Zn²⁺) and the silver-modified zeolite exhibited maximum metal adsorption with removal efficiencies of respectively - 97, 98, and 99% after 60 min making it appropriate for disinfection of water from bacteria and metal ions (Akhigbe *et al.*, 2014).

Silver clinoptilolite and heulandite were able to remove pathogenic fecal contamination bacteria *E. coli* and *Streptococcus faecalis* from water. The sodium form of the zeolite was prepared prior to the addition of AgNO₃. The highest elimination was achieved in silver-supported zeolite after 2 h of contact time, while sodium zeolitic mineral (no Ag content) didn't reveal any effect (Rivera-Garza *et al.*, 2000). Better elimination was achieved toward *E. coli*, with complete bacteria elimination with different Ag contents - A, 2A, 5A, and 24A. Regarding activity toward *S. faecalis*, complete elimination was achieved only with a concentration of 24A Ag content with at least 2h contact time. Under these conditions, the silver level in water remained at 50 µg/l. (Rivera-Garza *et al.*, 2000). Ivankovic *et al.* (2019) achieved complete elimination (90-100%) of hospital pathogenic carbapenem-resistant *A. baumannii* in experiments with real effluent wastewater. The treatment duration of 4 days ran in a bead filter system filled with silver-modified natural zeolite clinoptilolite. In a batch system, higher bacterial eradication was observed for treatment with silver-enriched zeolite with a minimal bactericidal concentration of 0.25-2 mg/L, in comparison to copper-exchanged zeolite, which required a minimal bactericidal concentration of 32-64 mg/L (-1) to achieve the eradication of log 5.6 log reduction (Ivankovic *et al.*, 2019). Silver and cetylpyridinium chloride-modified clinoptilolite exhibited greater activity against *P. aeruginosa* and *Bacillus subtilis*

in comparison to cetylpyridinium chloride-modified zeolite or other silver-modified zeolites in saline solution and distilled water (Malek *et al.*, 2014).

The silver concentration of silver-modified clinoptilolite–heulandite rich tuff toward *E. coli* (ATCC 8739) and total coliform microorganisms, as indicators of microbiological contamination of water were investigated in a continuous mode water system (synthetic wastewater or municipal wastewater, respectively). A concentration-dependent effect was observed on the microorganism and concentration in the effluent less than 0.6 µg/mL increased the bacterial survival percentage. The minimal concentration was therefore determined to be 0.6 µg/mL to eliminate the bacteria in the column system (De la Rosa-Gómez *et al.*, 2008).

Various materials incorporated with silver zeolites have been investigated, including zeolite/polymer composites, synthetic polymers, biopolymers, zeolite/textile composites, zeolite/metal coatings, dental materials, environmental/consumer materials (Dutta and Wang, 2019). Nanoporous zeolite modified by silver ions that could be applied in anticorrosive protective material, was deemed effective against *P. aeruginosa* bacteria (blue pus bacillus) (Znak *et al.*, 2021). Gelatin-based films containing silver clinoptilolite with a glycerol concentration of 25% and zeolite concentration of 0.5% resulted in films with more suitable properties for wound dressing applications. Gradual release of silver was achieved by immobilizing the Ag⁺ ions in supports that must be dispersed in the film used as a wound dressing (Hubner *et al.*, 2020).

Hernandez *et al.* (2021) tested stabilized organic nanoparticles (γ -sitosterol) and Ag cations on the external area of Ca-clinoptilolite zeolite. He determined wide antibacterial activity for a range of Gram-positive and Gram-negative bacteria, such as *A. baumannii* (17 mm) > *P. aeruginosa* (15 mm) > *Klebsiella pneumoniae* (11 mm). Gram-negative strains present the following sequence: *S. aureus* (15 mm) > *S. saprophyticus* (13 mm) > *E. faecalis* (12 mm) = *E. coli* (12 mm).

Yeasmin *et al.* (2016) used natural chabazite to develop antimicrobial powder-coated surfaces. Two types of chabazite were conditioned with sodium salt and functionalized with 0.05M solutions of Ag and Cu nitrates. Silver was utilized as an antimicrobial agent, whereas copper was used to prevent the reduction of silver during the coating process. These additives were used with a polyester resin system to produce ultrafine powder-coated

surfaces. These coated surfaces have shown homogeneous antibacterial properties with excellent durability against *E. coli*.

Clinoptilolite containing metallic Ag⁰ or Ag nanoparticles/clusters. The state of oxidation of the exchanged metal in zeolite could determine the microbicide effectiveness. The presence of silver in the zeolite could be in the form of Ag⁺ cations, metallic Ag⁰, Ag_n^{m+} clusters, and subcolloidal Ag. The microbicide effect of metallic silver and nanoparticles have similar to the silver ions mechanism. The proposed mechanism of action is due to direct contact-induced membrane damage and penetration of the cell, leading to leakage and cell death. They disturb cellular function by interacting with proteins, lipids, and DNA. In addition, reaction with the respiratory enzyme system leads to oxidative stress due to the production of - peroxide (H₂O₂), hydroxyl (OH[•]) and superoxide (O₂^{•-}) radicals. This in turn lead to cellular damage to proteins and nucleic acids. A number of factors influence the bactericidal effect of silver nanoparticles – their characteristics such as size, shape, dose, surface charge, etc. (Sutianingsih and Kurniawan, 2022). Bogdanchikova *et al.* (2000) used a sodium form of clinoptilolite to obtain silver clinoptilolite using 0.1M AgNO₃. Afterward, the reduction of silver was carried in a hydrogen flow at different temperatures from 20°C to 600°C. At temperatures below 200°C, small Ag₂⁺ dimers were formed. Subcolloidal silver particles were observed on an external clinoptilolite surface at 100°C. Reduction at higher temperatures >300°C K leads to the disappearance of silver clusters and subcolloidal particles and the formation of large silver particles on the external zeolite surfaces. The silver particles cannot be located in the zeolite cavities, which are much smaller (Concepción-Rosabal *et al.*, 2005). The average crystallite size of the cluster and nanoparticles is 4 nm and the largest uniformity is reported for hydrogen reduction at 100°C (Concepción-Rosabal *et al.*, 2008). The stability of natural clinoptilolite containing silver nanoparticles during storage in the air was found to be very high. The modifications performed on the zeolites allow controlling re-oxidation processes of these clusters and colloidal particles. The oxidation of clusters and colloidal particles leads to the reversible formation of Ag⁺ ions, which can be released to media in the usual way for zeolites through the mechanism of ion exchange.

Silver nanoparticles supported by natural Bulgarian zeolite clinoptilolite were effective and prevented *E. coli* strain 3398 cell growth when

added to peptone water in low amounts, thus suggesting application for water treatment (Panayotova *et al.*, 2018). They prepared Ag-clinoptilolite prepared by a two-step synthesis: Ag-form (Ag^+) followed by thermal reduction and formation of silver nanoparticles (Ag^0). Annealing temperatures of 400°C and 600°C reduced the Ag to metal Ag forming small (3-5 nm) nanoparticles and bigger (20-25 nm) on the surface of the zeolite. The silver-zeolite nanocomposite at a low amount added to peptone water, ceases the *E. coli* cell growth.

Silver nanoparticles on clinoptilolite loaded by ion exchange and wet impregnation were effective against *E. coli* Epi 300 and the effect was dependent on the concentration of the silver precursor used, the size of nanoparticles, and the leaching rate of silver ions (Missengue *et al.*, 2016).

Silver nanoparticles in natural zeolites (chabazite, clinoptilolite, and clinoptilolite-stilbite,) have been used for enhancing the antibacterial properties of commercial coatings, and have shown antibacterial activities against *E. coli* ATCC 25922, *K. pneumoniae* ATCC 25955 and *K. pneumoniae* ESBL+ bacteria (Torres-Flores *et al.*, 2021). The highest antibacterial activity of natural zeolite supported with Ag, Cu_2O , and ZnO was determined for the silver sample toward *Salmonella typhimurium* in contact with the zeolite in distilled water (Martínez-Vieyra *et al.*, 2021).

Silver nanoparticles (AgNPs) used for coating packed bed columns for water treatment were studied for their antimicrobial properties in different flow conditions and AgNO_3 concentrations (0.02, 0.04, 0.07, and 0.1 mM) and optimal conditions (flow rate of 1.5 L/h with AgNO_3 concentration 0.1 mM) achieved a high degree of bacterial removal from contaminated water - 99% for *V. cholera*, 93.7% for *E. coli*, 85% for *S. dysenteriae* and 77.5% for *P. aeruginosa* (Rashid *et al.*, 2021).

E. faecalis was found to be more resistant than *E. coli* to silver-modified zeolites of various particle sizes (Syngouna *et al.*, 2021). Particle size also affected antibacterial capabilities with higher removal rates observed for coarse (1–3 mm) than for fine (0–1 mm) zeolites.

However, Ag-based products possess some drawbacks where their effectiveness as an antimicrobial agent decreases in a solution containing electrolytes (Malek, 2014). Ag-based products can form insoluble precipitates such as AgCl and Ag_2S complexes when in contact with an electrolyte (chloride or sulphur anions) thus lowering their antibacterial activity (Xiu, 2011). In addition, silver

products can be inactivated during exposure to heat and light (Sutianingsih and Kurniawan, 2022).

Copper and Zn. Copper ions are also used for incorporation into zeolite as antimicrobial agents. Copper is toxic in small concentrations to bacteria and prevents their growth (Sani *et al.*, 2001). Copper oxide zeolite nanocomposites have been found effective against both Gram (+) and Gram (-) microorganisms (Alswat *et al.*, 2017). Cu-exchanged zeolite has been found effective against *E. coli*, but pure zeolite has been found ineffective (Milenković *et al.*, 2017). The advantage of copper over silver is better chemical stability and lower price. In comparison to silver, some studies have determined less activity. Antibacterial activity against *E. coli* involves diffusion through the plasma membrane of *E. coli* by the Cu^{2+} ions to be due to the neutralization of the negative charges of *E. coli* cell wall by Cu^{2+} ions due to electrostatic force, which leads to the destruction of the cell wall (Zhu *et al.*, 2017). Diffusion of Cu^{2+} due to different ion concentrations between inside and outside the plasma membrane of *E. coli* occurs. Once inside the cell, the metal reacts and interferes with the enzymes in the cell, by reacting with the (-SH) groups causing protein denaturation, and the result is interference in the growth and multiplication of the bacteria. The cell eventually dies as it loses its vital functions. Copper-loaded, plasma-treated natural zeolites showed inhibition zones toward *E. coli* and *S. aureus* (Montallana *et al.*, 2018). The mechanism of zeolite/zinc oxide nanocomposite for water cleaning has been found effective toward *E. coli* due to standard ion mechanism – penetration in the cell and causing osmotic pressure, causing bacterial death (Wangi *et al.*, 2020). According to Hrenovic *et al.* (2012) antibacterial activity of natural zeolite tuff containing 2.60 wt.% Cu^{2+} , 1.47 Zn^{2+} , or 0.52 Ni^{2+} was highly effective against *E. coli* (strain DSM no. 498) and *S. aureus* (strain DSM no. 799) in a model of effluent wastewater and synthetic wastewater. Since highest antibacterial activity was detected in a model of effluent wastewater with copper natural zeolite, where no Cu^{2+} leaching was observed. The author suggested the bactericidal activity was due to the metal ions and no leaching is necessary, since the bacteria makes direct contact with the ion (Hrenovic *et al.*, 2012). Low leakage was observed for Zn natural zeolite, and antibacterial activities of both Cu and Zn zeolites reduced the bacterial number for six magnitudes in effluent wastewater, making them good candidates for antimicrobial agents for water treatment. Natural zeo-

lite clinoptilolite modified with Cu^{2+} was inhibiting against *C. albicans* (44.24%), *S. aureus* (59.26%), and *E. coli* (100%). Zn activated clinoptilolite was less effective against the same bacteria with inhibition % of *C. albicans* (33.81%), *S. aureus* (5.56%) and *E. coli* 76.24%.

Hrenovic *et al.* (2012) proposed to use natural zeolite tuff with 70% clinoptilolite content for removal of heavy metals from polluted water. The antibacterial activity of the zeolite containing 2.60 wt.% Cu^{2+} , 1.47 Zn^{2+} or 0.52 Ni^{2+} were tested. The Ni-modified zeolite showed high leaching of Ni^{2+} and weak antibacterial activity. On the other hand, Cu and Zn zeolites showed antibacterial activities of the zeolites against *E. coli* and *Staphylococcus aureus*.

Copper, zinc-containing, and silver heulandite-clinoptilolite have been deemed bacteriostatic toward Gram-negative bacterium *E. coli*, Gram-positive bacteria *S. aureus*, and *B. subtilis*. The activity was less for Zn and Cu compared to Ag zeolite. However, zinc-modified zeolite was found to possess activity against *B. subtilis* and was deemed inactive against *E. coli* and *S. aureus* (Tsitsishvili *et al.*, 2021). Zn-exchanged zeolite composed of ($\approx 70\%$) clinoptilolite and mordenite revealed an effect on *Helicobacter pylori* and achieved an effective MIC of 4 mg/mL (Cerri *et al.*, 2021). Also, Zn-bearing clinoptilolite was tested *in vivo* on the effect of cecal microflora of broiler chickens, and the antibacterial effect was observed against *Salmonella enterica Pullorum* infection (Wang *et al.*, 2013), as well as toward *E. coli* (Tang *et al.*, 2014).

Zn, Ag, or Cu-modified zeolite was tested against marine microorganisms (*E. coli* and *A. baumannii*). Out of them, Ag and Cu-charged zeolite revealed a bactericidal effect. Ag-zeolite displayed the strongest effect after 3 hours' exposure, followed by Cu after 6 hours. However, Zn-modified zeolite lacked bactericidal activity after 24 hours of exposure, even though it possessed antibacterial effects (Dikića *et al.*, 2019).

Antifungal activity of natural and modified zeolites

Every healthy human is confronted with thousands of fungal spores every day without developing diseases (Goffeau, 2008; Fisher *et al.*, 2012) because the spectrum of diseases caused by fungi is dependent on the health of the immune system. In immunocompromised individuals, infections caused by fungal pathogens such as *Candida sp.* or *Aspergillus sp.* can lead to disease and even death (Brown *et al.*, 2012). In recent years, severe fungal infections have substantially contributed to the

increased morbidity and mortality of immunocompromised patients (Pfaller and Diekema, 2007; Person *et al.*, 2010). Examples of disease states caused by fungi include mold allergies and cutaneous dermatophyte infections (ringworm) (Ribes *et al.*, 2000; Gow *et al.*, 2002) For example, fungi are able to produce mycotoxins, which are secondary fungal metabolites and are toxic to humans, animals, and plants. The majority of mycotoxins like aflatoxins, citrinin, patulin, penicillin acid, tenoisonic acid, ochratoxin A, cytochalasins, deoxynivalenol, fumonisins, fusarin C, fusaric acid, and zearalenone are produced by three fungal genera: *Aspergillus*, *Penicillium*, and *Fusarium* (Kuhn and Ghannoum, 2003). These species produce conidia that are released into the atmosphere and are among the most important pathogenic fungi. *Aspergillus niger* is a mold that is reported as a cause of pneumonia (Person *et al.*, 2010). Aspergilloma, invasive aspergillosis, allergic bronchopulmonary aspergillosis, ocular infections, sinusitis, otomycosis, cutaneous aspergillosis, osteomyelitis, endocarditis, urinary tract infection are diseases caused by *Aspergillus spp.* (Nariman-Shahhosseini *et al.*, 2011). The most common cause of fungal infections remains *Candida albicans* (Kabir and Ahmad, 2013). *Candida spp.* represent one of the most common pathogens which are responsible for fungal infections often causing hospital-acquired sepsis (Patterson, 2007; Trofa *et al.*, 2008). *Candida spp.* isolated from hospitalized patients accounted for 15.5% of *Candida* isolates in North America, 16.3% in Europe, and 23.4% in Latin America (Messer *et al.*, 2006). The first step in pathogenesis is the colonization of the skin or gastrointestinal tract (Benjamin *et al.*, 2000). These fungi typically enter the body as spores or, possibly, mycelial fragments via the lungs (Trofa *et al.*, 2008). *Candida spp.* causes acute neutrophilic meningitis, chronic lymphocytic meningitis, and granulomatous meningitis (Chakrabarti, 2007), fungal peritonitis (Wang *et al.*, 2000), fungal arthritis (Cuende *et al.*, 1993; Legout *et al.*, 2006), ocular infections (Rosen and Friedman, 1973), otomycosis (Vennewald *et al.*, 2003), onychomycosis (Segal *et al.*, 2000), vulvovaginitis (Weems, 1992).

Antifungal properties of metal ions

The antimicrobial properties of silver have long been known. Thanks to silver ions and silver nanoparticles, the solution called "Holy Water" has antiviral, bactericidal, and antifungal effects (Mikhailova, 2020). Silver can inhibit microorganisms in many different ways and can be used to control the growth of fungi. The antimicrobial

mechanism of the Ag nanoparticles has not been fully understood. Silver nanoparticles can bind to the wall of the fungal cell, damaging cell membranes, making them porous (Kim *et al.*, 2009) and after that penetrate inside the cell, causing structural changes. One possibility of these structural changes may be associated with the formation of free radicals from the surface of Ag. Damaged cell membranes will facilitate the reaction of silver nanoparticles with cellular DNA and lead to problems with fungal DNA replication, leading to fungal death (Marambio-Jones and Hoek, 2010).

Copper is one of the essential elements needed by organisms. This element has many functions in biological cycles. When photochemical processes occur in the presence of copper, ROS like superoxide radicals and hydroxyl radicals can be produced. The fungicidal properties of copper have long been known. In the 1880s, the use of a lime-copper mixture, known as the “Bordeaux mixture”, began in agriculture as a fungicide (La Torre *et al.*, 2018). There are many studies on the antifungal activity of copper (Medina-Ramírez *et al.*, 2022). The spectrum of action of copper compounds makes this metal one of the main components of fungicides worldwide. Copper ions act on the cell membrane, causing the denaturation of structural and enzymatic proteins and this leads to a change in the semi-permeability of the membrane. Inside the cells, copper can confuse many enzymatic reactions and inhibit the germination of spores (La Torre *et al.*, 2018).

All forms of life, from bacteria to humans, need iron to grow. This element is one of the most abundant in the earth’s crust. Iron is an important element in many biochemical reactions due to its easy ability to gain and lose electrons. At the same time, this transition metal exhibits antimicrobial properties, destroying the cytoplasmic membrane of the cell (Rice, 2018). The antifungal properties of iron have long been used. Win *et al.* (2021) reported that iron oxide nanoparticles exhibit antifungal activity against numerous fungal pathogens and can be used to control different fungal diseases. Fe (Fe_3O_4 and/or $\gamma\text{-Fe}_2\text{O}_3$) and silver nanocomposites showed significant antifungal activity against four *Candida* species (Prucek *et al.*, 2011). ROS can be generated by various reactions occurring in the presence of iron and copper, such as Fenton and Fenton-like reactions, resulting in the oxidation of biomolecules.

Zeolite like an antifungal agent

Over the last two decades, several studies

have shown that both synthetic and natural zeolites are used as sorbent material and their charged cations can be exchanged with metal ions to add antimicrobial properties (Niira *et al.*, 1990; Odabas *et al.*, 2011). Septommy *et al.* (2020) demonstrated that antifungal agents can be obtained by modifying natural zeolite with silver metal. The antimicrobial potential of silver zeolites was assessed using bacteria and yeast as sensitive indicator strains. Good properties of silver zeolite against widespread microorganisms have been reported by Ferreira *et al.* (2012). Septommy *et al.* (2020), demonstrated that natural zeolite, modified with silver showed an antifungal effect against *C. albicans* and *Saccharomyces cerevisiae*. Good results are also obtained when combining zeolite with copper ions. Cu^{2+} -exchanged zeolite with Cu showed excellent antifungal activity against *Fusarium graminearum* (Savi *et al.*, 2018), *A. niger*, *A. fumigatus*, *Mucor hiemalis*, *Penicillium griseofulvum* (Nikolov *et al.*, 2023), *A. flavus* and affect conidia germination (Savi *et al.*, 2017). *A. fumigatus* was influenced by the Fe-modified zeolite for up to 7 days (Nikolov *et al.*, 2023). According to the International Agency for Research on Cancer (IARC 1993), aflatoxin B1, produced by *A. flavus*, is the most common and potentially carcinogenic mycotoxin. Zeolites are used as adsorbent materials capable of bonding mycotoxins effectively (Papaioannou *et al.*, 2005).

Antiviral properties of zeolites

In addition to their well-studied antibacterial and antifungal properties, zeolites also have potential antiviral or to be more precise, virucidal properties, depending on the preparation and structure of the given zeolite. Enveloped viruses are more susceptible to the environment than non-enveloped viruses (Watanabe *et al.*, 1989; Barker *et al.*, 2001). Viruses could also be immobilized on a zeolite-covered surface without requiring a metabolic process (Thurman *et al.*, 1989). Biocompatible, possessing both high chemical selectivity and absorption potential while being generally safe and non-toxic, zeolites have attracted significant interest for application within the biomedical field, more so since the possibility to synthesize them with regular micropores, further stabilized in colloidal suspensions, thus making them suitable for adsorbing different molecules/particles based on size, including viruses if the pores are of suitable size. This custom “tailoring” of zeolites, theoretically allows them to be adapted, so to speak, to any number of chemical environments, giving them stability in alkaline or acidic media, allowing the designer of the

zeolite to give them different properties by adding metal cations, modifying their absorption capacity, affinity, etc., making them a prime potential candidate for antiviral use (Sellaoui *et al.*, 2021). A study was done by Bright *et al.* (2009), in which sodium aluminosilicate powders with amended metal ions and zeolites containing silver and copper ions were used against human coronavirus 229E, FIPV (Feline Infectious Peritonitis Virus) and Feline Calicivirus F-9 leading to significant reductions of 229E after 1 hour of zeolite-virus suspension. Silver-copper containing zeolites, while incorporated into plastics, lowered the viral titer within 24 hours. Their study noted that the used zeolites were effective against enveloped and non-enveloped viruses (Bright *et al.*, 2009).

It's likely toxicity in complex organisms could be due to high contents of heavy metals like Pb, Cd, Zn, Cu, etc., which is a hurdle for zeolites in general when considered for medical applications. However, a study carried out with mice (6 months) and rats (12 months), showed that taking clinoptilolite orally caused no changes that could be considered toxic, for the duration of the study (Grce and Pavelic, 2005).

Grce and Pavelic (2005) conducted a study on four different viruses, based on their characteristics, DNA/RNA, with or without a lipoprotein envelope acquired from the host cell and its infectivity and rapid CPE (Cytopathic Effect) in cell culture. Human adenovirus 5, herpes simplex virus type 1 (HSV 1), and human enteroviruses (coxsackievirus B5 and echovirus 7) were used. It was determined that the effectiveness of clinoptilolite on viral replication depends on the concentration of the zeolite and the viral titer (**a viral titer is an approximate concentration of viral particles after a virus has been cultivated and harvested*). The best antiviral effect was shown with the highest concentration of clinoptilolite and the lowest viral titer used, demonstrating an inhibitory effect of the used zeolite, albeit virus-type and zeolite concentration dependent. The study proposes 2 mechanisms of action for the zeolite: viral inhibitions are probably unspecific and independent of virion size, structure, and genome type (Grce and Pavelic, 2005). Microporous zeolites can and often do absorb essential minerals and amino acids from culture media due to proximity. The second proposed mechanism of action, according to Grce and Pavelic (2005), is the ion exchange capability of zeolites that is capable of destabilizing the morphology of viral particles. The lipoprotein structure (viral capsid) is more suscep-

tible to environmental factors, which could explain why herpesviruses were more destabilized than adenoviruses in their study. A hurdle in their theory however, an inhibition effect was also observed in non-enveloped viruses such as *coxsackievirus B5* and *echovirus 7*, furthermore, non-enveloped viruses were equally inhibited by the microporous zeolite.

A possible mechanism of action of ion-containing zeolites, such as clinoptilolite, is based on the effect released cations have on DNA/RNA replication, both viral and cellular, as well as their effect on the viral capsids itself if present. Thurman describes 3 possible mechanisms of action for silver ions in his 1989 paper (Thurman *et al.*, 1989). DNA binding, interactions with the cell membrane, and electron transport interference. Silver completely binds to proteins when applied topically, however, it does require a long contact time for disinfection since it does not enter the cell (Rahn and Landry, 1973). Its use as a disinfectant is attributed to the ease with which it forms insoluble compounds with anions, enzymes, and biological materials (Thurman *et al.*, 1989). Since protein denaturation is more difficult than metal oxidation, the quantity of silver ions needs to be quite high when dealing with viruses compared to bacteria (Thurman *et al.*, 1989). Furthermore, silver can bind with DNA, increasing the rate of dimerization. Rahn and Landry in separate studies proved this using phage DNA and UV irradiation (Rahn and Landry, 1973; Rahn *et al.*, 1973a). In addition, silver can also bind with electron transport groups that have sulfur, nitrogen, or oxygen atoms (Thurman *et al.*, 1989). Thiolated nucleotides are generally highly specific centers for stable heavy metal attachment. Metal binding to a polynucleotide decreases the melting temperature by hindering hydrogen bond interactions if the metal ions bind bases and form cross-links between bases (Thurman *et al.*, 1989). When DNA-silver complexes occur at bases, causing denaturation by displacing hydrogen bonds between adjacent nitrogens of pyrimidines and purines, preventing replication from occurring (Richard *et al.*, 1973).

Another metal of note is Copper. Copper typically occurs as Cu^{+2} outside the cell and Cu^{+} inside the cell. Metal ions may function as either Lewis acids (atoms, ions, or molecules open to accepting ions) or bases when present as metal complexes, thereby enhancing displacement reactions. The proton provides a reaction pathway of lower energy by withdrawing electrons and weakening the bond to be broken. Metals can facilitate hydrolysis or

nucleophilic displacement either directly, through polarization of the substrate and subsequent external attack by the nucleophile (hydroxide radical), or indirectly, through the generation of a coordinated reactive nucleophile. At pH > 10 Cu⁺² chelates to the ribose rings of ATPs, which leads to Cu⁺² hydrolyzing to ADP + phosphate in a neutral solution. Martin and Mariam showed that Cu⁺² can reversibly denature DNA in low ionic strength solutions in which copper ions interfere with the formation of hydrogen bonds (Thurman *et al.*, 1989). High concentrations of Cu⁺² increase the disordering of poly A and poly C segments of polynucleotides from double to single-stranded (Rifkind *et al.*, 1976). If a nucleic acid helix is stabilized or destabilized by chelation with metal ions, replication and/or transcription may be altered if normal DNA unwinding is affected, or if the nucleic backbone is hydrolyzed, which is why copper, even in slight to moderate concentrations is harmful. Copper, and by extension metal ions in general, are likely to form connections due to their positive charge. Metal ions can stabilize or destabilize proteins and enzymes, altering their function, and activating or deactivating them on a case-by-case basis, which can have dire consequences for the well-being of the cell. Virucidal effects were displayed by Cu and Ag-modified clinoptilolite (Nikolov *et al.*, 2023).

In theory, the porous and modifiable structure of zeolites makes them a promising tool for immobilizing and potentially neutralizing viral particles.

While a promising prospect is to be added to the antiviral arsenal of drugs, further studies are required on clinoptilolite and other zeolites in general to discover a viable antiviral agent.

Conclusion

Numerous studies mentioned in this review showed that natural zeolites and their modified form are effective against microorganisms. The antimicrobial approaches using natural zeolites are mainly focused on cation release modifications obtained by different procedures resulting in modified zeolite containing cations, nanoparticles or nanocomposites with a microbicide effect. The mechanism of microbicidal action of the modified zeolites includes: direct contact-induced membrane damage and penetration; disruption of the bacterial cell wall and membrane; disturb cellular function by interaction with proteins and DNA; reaction with respiratory enzyme system i.e., oxidative stress (Fig. 1).

Antimicrobial properties, high efficiency and environmental production outline the potential of modified natural zeolites as functionalized materials in the global fight and prevention against pathogens.

Acknowledgements

The results of this work have been achieved in fulfillment of a project financed by the National Science Fund of Bulgaria under contract No. KII-06-M47/1 from 26.11.2020.

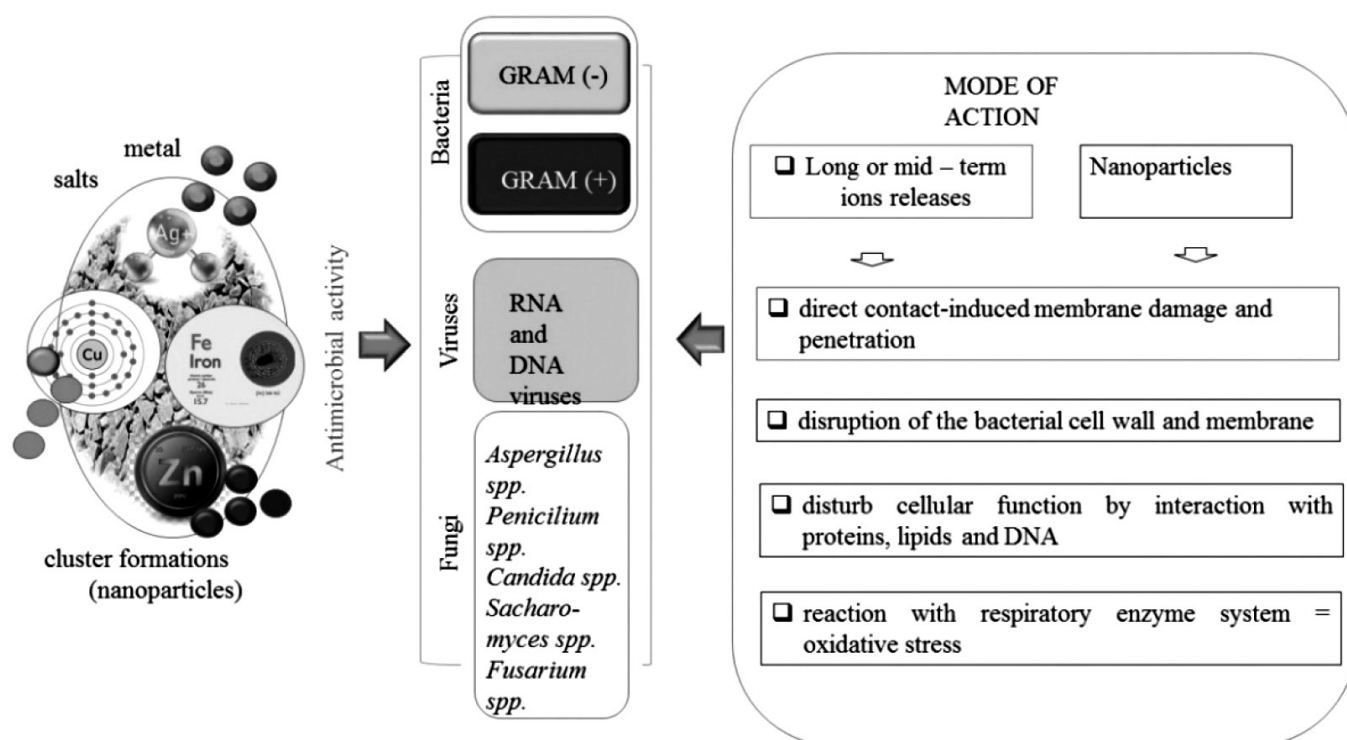


Fig. 1. Mode of microbicidal action of modified natural zeolites

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