Review

Biomedical applications of zeolite-based materials: A review

Author links open overlay panelHamed Serati-Nouri [a] [b], Amir Jafari [c], Leila Roshangar [a], Mehdi Dadashpour [a], Younes Pilehvar-Soltanahmadi [d], Nosratollah Zarghami [a] [e]

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Highlights

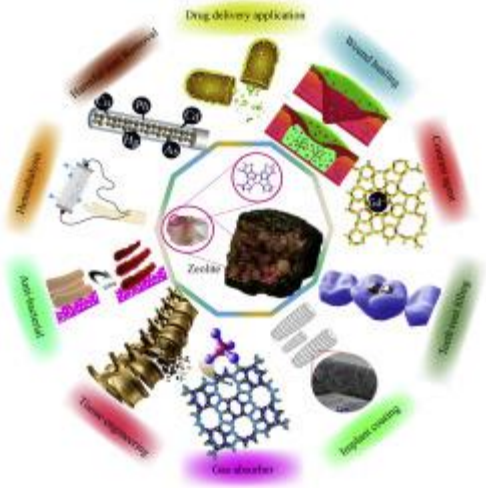
- Zeolites are antibacterial, biocompatible, non-toxic and highly absorbent substances
- Zeolites in conjugation with polymers have been used various biomedical applications
- Zeolite in combination with drug-loaded polymers facilitate prolonged drug release
- Zeolite-based biosensors have been designed to detect cancer biomarkers
- the application of zeolite in biomedicine is expected to grow in the coming decades

Abstract

Zeolites are crystalline, hydrated aluminosilicates of alkali earth cations, consisting of 3D frameworks of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedral, linked through the shared oxygen atoms, which have been widely applied in multifarious technological approaches such as adsorbents, catalysts, ion exchangers, molecular sieves for separation, and sorting the molecules according to their crystalline size dimensions. On the other hand, the unique and outstanding physical and chemical properties of zeolite materials such as porous character, ion exchangeability, water absorption capacity, immunomodulatory and antioxidative effects, biocompatibility and long-term chemical and biological stability, make them increasingly useful in various filed of biomedicine including drug delivery systems, wound healing, scaffolds used in tissue engineering, anti-bacterial and anti-microbial, implant coating, contrast agents, harmful ions removal from the body, gas absorber, hemodialysis, and teeth root

filling. Therefore, this review focuses on the more recent advances of the use of zeolites in various biomedical applications feedbacks especially drug delivery, regenerative medicine, and tissue engineering with special emphasis on their biomaterial perspectives.

Graphical abstract



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Keywords

Zeolite
Nanomaterials
Regenerative medicine
Drug delivery
Tissue engineering

1. Introduction

Zeolites in terms of elements formed from atoms of phosphorus, aluminum, oxygen, and silicon that intrinsically embedded a regular structure with repeated topology [1]. The term “zeolites” backs to 1756, the time when Swedish mineralogist Axel Fredrik Cronsted discovered Stilbite. Zeolites could be defined as porous aluminum silicates. Structurally zeolites are porous crystalline solids with a well-defined structure and framework. By looking at zeolites interconnected network, oxygen atoms located in the corners of the four-sided network and silicon or aluminum atoms in the center [2]. Zeolites are classified into synthetic and natural types in that synthetic zeolites obtained from the combination of certain substances through the fast formation. As could be seen in Fig. 1, there are a few techniques for synthesizing zeolites either small or large crystalline sizes in a short time *via* alkaline environments recruitment and hydrothermal conditions (100–200 °C) [1]. However, natural zeolites have been obtained over the millions of years from sea salt and ash of activated volcanoes have a

larger grate particle size than synthetic zeolites (Fig. 2) [3]. The two atoms of silicon and aluminum are two integral atoms of zeolites. Zeolites classification can go beyond the origin and based on their adapted structures can be classified too in which up to now 200 types of synthetic zeolite structure and 10 structure types of natural zeolite have been discovered. Each one of these structures includes one or more zeolites; for example, Faujasite (FAU) structure contains two types of zeolites: zeolites Y and X, each of them has their own distinct physical and chemical properties. Therefore, the application of synthetic or natural zeolites will be dependent on the desired physicochemical properties, which may be dependent on the function of A) crystalline structure B) chemical composition of zeolites [4].

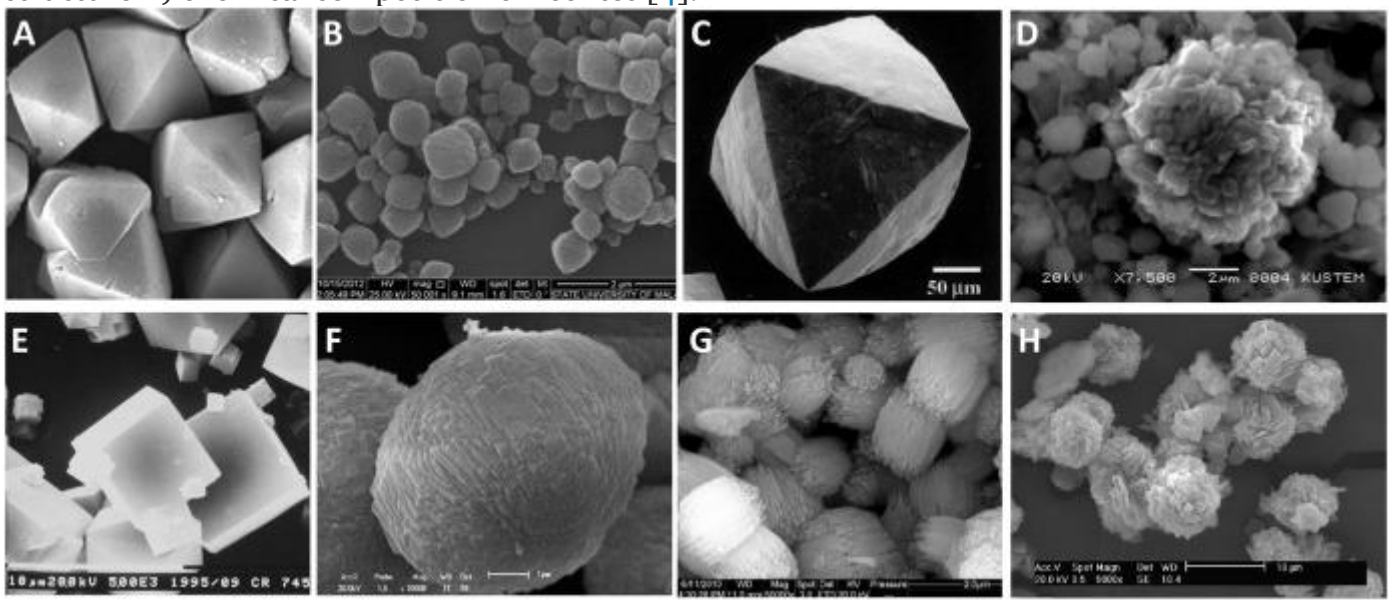

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Fig. 1. Scanning electron micrographs of common synthetic zeolites. (A) Zeolite Faujasite, (B) Zeolite Beta, (C) Zeolite X, (D) Zeolite Y, (E) Zeolite A, (F) Zeolite ZSM-5, (G) Zeolite Mordenite, (H) Zeolite P.

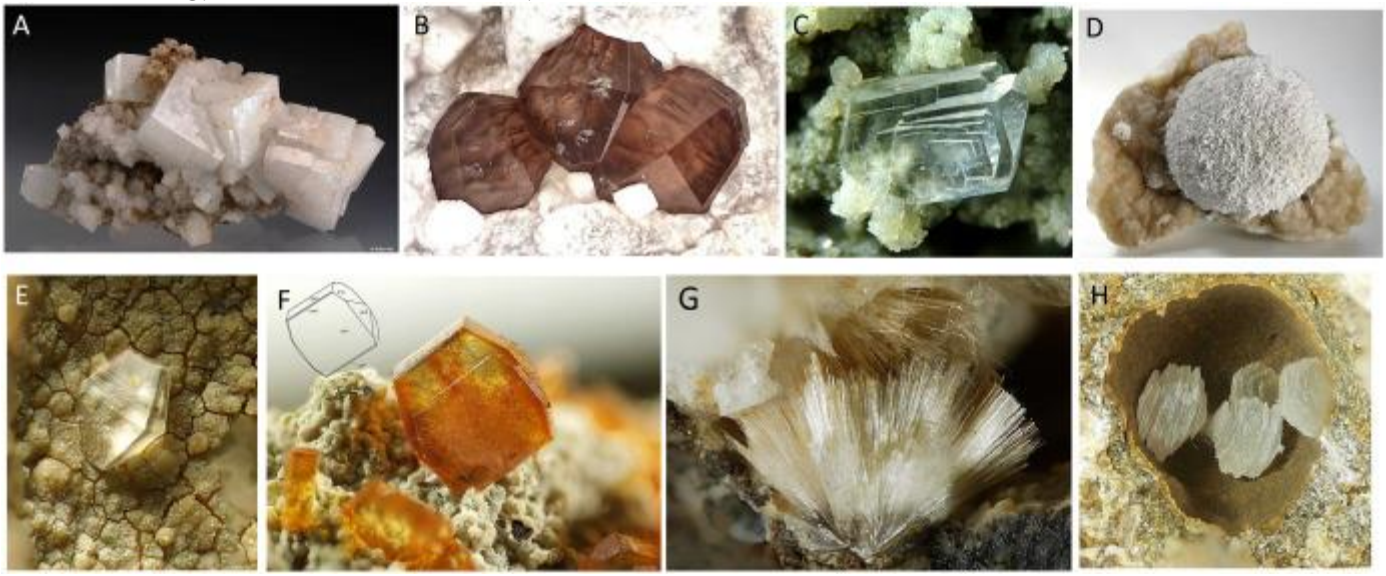

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Fig. 2. different morphology of common natural zeolites. (A) Chabazite, (B) Analzime, (C) Clinoptilolite, (D) modernite, (E) smectite, (F) Stilbite, (G) phillipsite, (H) Erionite.

Zeolites are edible, biocompatible, and possibly non-toxic substances and they have a few unique features like molecular sieve structure, ionic exchangeability, and water absorbent. Hence, these properties account for their diverse applications in several medical areas. By considering natural zeolites such as Clinoptilolite by way of food additive provides essential minerals for individuals, and also must be implied that it prevents humans from being poisoned by harmful substances in the environment, air, water, and food [5,6].

In recent years, an increasing number of scientific literature has shown the adapted/tailored biological behavior of zeolites [7,8]. Due to zeolites biocompatibility, researchers in 2014 demonstrated that human bone marrow stromal cells (hBMSCs) which cultured on the surface of synthesized ZSM-5 zeolite; hBMSCs were adhered, morphologically were expanded and proliferated over the time, so the number of live cells on ZSM-5 zeolite increased steadily. Besides, there were not any morphological changes in cells [9,10]. Moreover, the presence of special nanomaterials like Silver nanoparticles, zeolite biocompatibility suggests that Ag-Nano-ZSM-5 had no toxicity for RAW 234.7 macrophage and CaCo2 cells and possibly had enormous potential for biomedical applications in bone implants [[11], [12], [13]]. On the other hand, zeolites are well-known for their ions and toxic materials adsorption; in fact, crystalline structure with tiny and interconnected negatively charged channels facilitates absorbing all positive-charge materials/ions. For most of the poisonous substances that have positive charges and these toxic substances could be trapped in zeolite canals. Also, this property is used to absorb the radioactive material of the Chernobyl power plant catastrophe [14]. Thomassen *et al* synthesized nanozeolite A and Y types with the size range of 25–100 nm, and toxicity evaluation represented no significant toxicity for nano-zeolite at 500 μg/ml concentration range [15].

In addition to mentioned issues for zeolites also they have a unique molecular sieve so that after heating and dehydration of zeolite, gases with smaller molecular volumes and diameters can pass through the associating channels in its crystalline network, but larger cations and gases will not be able to cross the diameter of the desired crystalline zeolite networks. In this regard, a mixture of several molecules with different sizes could be separated. For example, if air which is a mixture of oxygen, nitrogen, and carbon dioxide gases passes through a part of the clinoptilolite zeolite, oxygen passes through it and separates from nitrogen and carbon dioxide in which produce pure oxygen for medical use from the air [16,17]. To the best of our knowledge about loading and releasing specific ions or molecules inside the body, zeolite intelligent ion-exchange property, in this way Mendeleev table could go through with this framework. In other words, zeolite can be used as the carrier of essential elements for mineral deficiency in malnutrition patients and thereby introduce new insights for delivering molecules with potential carrier's applicability. The crystalline structure of zeolite constitutes from primary chemicals that don't decompose into another composition in normal condition for this reason they've called permanent compounds [18]. Since more than 70% of the body includes fluids form water, zeolites can be used to control the body fluids volume [19]. In this approach, zeolite is used as an anti-diarrheal drug, which is also useful for digestive disorders. For proof of concept, in a study, zeolite clinoptilolite was used to improve the calf's diarrhea. For one kilogram of calf weight, one gram of zeolite is mixed with milk and fed to calves to improve immunity and cure calf diarrhea [20,21]. About the

applicability of natural zeolite to some extent, it has been argued that these materials moderate the pH level of the body to its normal range and reduce the negative effects of body low pH than the normal range. As has been discussed before in several articles, excessive pH (H+ cation) facilitates the prerequisite conditions for cancer, reduces brain activity, as well as depression, anxiety, delusion, and anesthesia [19]. According to the aforementioned issues, so far, several studies have been investigated the application of zeolites in various medical fields, which we will overview based on the published papers. Besides, we will discuss zeolite applications in biomedical sciences and bone tissue engineering and the relationship of them with regenerative medicine in detail.

2. Physical, chemical and morphological characteristics of zeolites

An aluminosilicate framework is an elementary structure of all zeolite-based material which contains a tetrahedral arrangement of silicon cations (Si^{4+}) and aluminum cations (Al^{3+}), which are surrounded by four oxygen anions (O^{2-}), as a result, the macromolecular three-dimensional framework of SiO_2 and AlO_2 tetrahedral building blocks form silicate tetrahedra structure [22].
The primary building units and secondary building units are the zeolite's crystal structures components. The primary building units are the $(SiO_4)^{4+}$ and $(AlO_4)^{5+}$ tetrahedra. Through sharing oxygen atoms with an adjacent tetrahedral, special arrangement of simple geometric created. Furthermore, secondary building units have different types including single rings, double rings, polyhedra, or even more complex units that are linked together in various ways to produce a unique system of channels and cages that made them suitable for specific medical or industrial utilization [23].
Different types of zeolites naturally show different morphology (Fig. 2). Clinoptilolite and heulandites are examples of isostructural and both mostly occur as plates or laths with tabular form. Mordenite generally comprised of fine fibers or as thin laths and needles. Chabazite has a cube-like appearance because of its rhombohedral secondary building units [23,24].

3. Applications of zeolites

Diversity of zeolite structures rise from the pore size variation (between 2 up to 13 A°), variation in shape with 4–12 loops and internetwork connection have made zeolite one of the useful substances in different applications [19]. Zeolites have a great potential for a wide range of technical, industrial, agricultural, commercial, and also biomedical applications; for this reason, zeolites have been called “magic stones” [25]. Synthetic zeolites mostly have been applied in industry. On the other hand, the lower price of natural zeolites in comparison with synthetic ones caused the replacement of synthetic zeolite with natural one and paves the way for its development in the market [19]. Previously, natural zeolites have been used in the cement industry as fillers [26,27]. Clinoptilolite is used in agriculture as a potassium releasing agent and prolongs the irrigation time due to its good absorbent property [28,29]. Furthermore, natural zeolites are being used for wastewater treatment and elimination of the soluble heavy metals [30,31]. Today, large amounts of zeolites have been exploited in the detergent industry [32].

Zeolites counted as one of the efficient catalysts for many organic reactions and with diverse structures to accelerate chemical reactions and also applicated as absorbent and drying agents. Much of the gasoline and petrochemicals in the world are produced through zeolite catalysts [33]. One of the enormous interests in applications of zeolites refers to biosensors [34,35]. Over the past few years, most of the scientific literature have focused on harnessing zeolite-based materials to the benefit of the medicine. The purpose of this research is to summarize various fields of zeolite applications in modern medicine as well as its usage in the improvement of medical equipment, substances, and drugs. In this study, zeolites are classified into the types of their applications in medical-related fields up on to their biological, physical, and chemical properties. In this context, it is possible to facilitate the selection of appropriate zeolite according to the application in the medical sciences. Thereby, the applications of zeolite in the field of modern drug delivery systems wound healing, engineered scaffolds for tissue engineering, anti-bacterial agents, implant coating, contrast agents, removal of harmful ions from body, hemodialysis and root canal filling of teeth were discussed. In Table 1, the different structures and types of zeolites as well as their medical applications that have been carried out up to now, have been summarized.

Table 1. Medical applications of natural and synthetic zeolites.

Empty Cell	**Structure**	**Zeolite type**	**Applications**	**Ref.**
Natural	HEU	Clinoptilolite	Tocopherol absorbent	[34]
			Carrying out metronidazole, sulfamethoxazole, and aspirin	[35]
			The carrier of ibuprofen	[46]
			Removal of Cephalexin from aqueous solution	[48]
			Provides support for the release of diclofenac	[38]
			Anti-cancer agent	[58]
			Improve the antibacterial properties	[73]
			Dexamethasone absorber to remove it sewage	[94]
			Ability to store and release tetracycline	[40]
			The ability to simultaneously load silver ions and sulfadiazine	[49]
Synthetic	BEA	Beta	Improve the penetration of both salbutamol and Euphyllin to treat asthma	[51]
			Carrier of 5-fluoroacetic anticancer drug	[53]
			Absorption of uremic toxin and removal of blood for hemodialysis	[95]
			Shell to protect Doxorubicin	[49]
	FAU	Faujasite	Carrier of CHC anticancer drugs	[57]
			Wound healing	[57,67]
		X	Ability to release ketoprofen	[39]
			Tetracycline carrier	[41]

Empty Cell	Structure	Zeolite type	Applications	Ref.
			Cyclophosphamide carrier	[44]
			The carrier of ibuprofen and indomethacin for anti-inflammatory effect	[45]
			Release control of anti-malaria drug chloroquine	[52]
			Carrier of 5-fluoroacetic anticancer drug	[53]
			Ability to release folic acid through an electric field	[42]
			The ability to simultaneously load silver and sulfadiazine ions	[43]
			Carries of ibuprofen and indomethacin for anti-inflammatory effect	[45,47]
		Y	Carrier of 5-fluoroacetic anticancer drug	[55]
			Scaffolds for bone tissue engineering	[64]
			Improve the antibacterial properties	[71,72,74]
			Improved the resolution of MRI imaging	[[87], [88], [89]]
			Absorber of H2S gas and harmful gases	[92]
			Ability to release ketoprofen	[39]
			As a capsule for CHC anticancer drug	[57]
			Bleeding control and wound healing	[62]
	LTA	A	Improve the antibacterial properties	[75,77]
			Coating of Titanium surfaces	[82,84]
			Improved the resolution of MRI imaging	[87]
			Gas absorbent of oral H2S	[91]
			Gentamicin loading and delivery ability	[24]
			Improve the antibacterial properties	[24]
			Absorbent of famotidine ulcer drug	[50]
	MFI	ZSM-5	Carrier of 5-fluoroacetic anti-drug	[56]
			Covering titanium surfaces	[83]
			Gas absorbent of oral H2S	[91]
			Absorption of uremic toxin and removal of blood for hemodialysis	[95]
			Absorbent of famotidine ulcer drug	[50]
	MOR	MORDENITE	Absorption of uremic toxin and removal of blood for hemodialysis	[95]
	GIS	P	Release control of anti-malaria drug chloroquine	[52]

3.1. Zeolite application in drug delivery systems

One of the most important factors in tissue engineering is pertinent with delivering growth factors to the targeted cell in which it seems without an appropriate delivery system it wouldn't be efficient [[36], [37], [38]]. Suggested strategies were including the adaption of inorganic/organic nanoparticles such as liposomes, polymersomes, and dendrimers in which pushes the frontier of the drug delivery science edges [[39], [40], [41]]. Because of the aforementioned disadvantages of nanoparticles like low specificity, poor solubility, rapid drug clearance, or biodegradation, and also limited targeting are main problems that restrict drug delivery to the desired site [42,43]. However, nanomaterial optimized sizes that going to get through the smallest capillary vessels with taking advantage of high drug loading capacity, high surface to volume ratio, various routes of administration including oral, nasal, parenteral, and intra-ocular were led to the prevention of rapid clearance [[44], [45], [46]]. Zeolite by having a small porous cavity in comparison with other mesoporous material in conjugation with features like drug molecules size screening (*i.e.* shows size selectivity) for adsorption into the pores and release of the molecules in the matrix is controlled by. Drug-zeolite in combination with biodegradable polymers (chitosan, gelatin, and alginate) facilitate prolonged drug release [47]. Besides, advancements in combining a mixture of polymers for improved biodegradability enhanced stability through coatings/surfactants, controlled release properties, long-circulating *via* altering charges, improving efficacy without the need to higher doses, and surface characteristics for attaining both active and passive drug targeting are the most important features of nanoparticles application as novel drug delivery system [48,49].

Recently new functionalized or neutralized bioactive nanofibers have opened up new insights in regenerative medicine and drug delivery systems; fibers functionalization in a way that core remains unaffected by the fiber chemistry providing a great opportunity for delivering a drug, gene, growth factor, nutrition and biomolecules in a sustained manner with the prevention of microenvironments unstable biological agents. In polymer-based drug delivery and tissue engineering research, most of their progressions owned to biodegradable polymers features in comparison with non-degradable polymers [50]. Polyethylene glycol (PEG), polyglycolic acid (PGA), polylactic acid (PLA), and their combinations with other polymers made it possible for the generation of new nanocarriers, which sometimes use hydrogels in their design [51,52]. In term of the developmental aspect of drug delivery especially with nanoparticles, but novel platforms like ‘smart’ or ‘stimuli-responsive’ polymers might show predicted responses according to nature or design plan that had been applied like shrinkage or swelling, temperature change, pH and magnetic field [53,54]. In this way, there has been a dramatic development in the production of human medicines with the use of a mixture of drug substances with clinoptilolite and synthetic zeolites [55].

Some drugs and vitamins that absorb in the intestine, are sensitive to acidic pH of the digestive system; therefore, through a study which conducted on tocopherol absorption (*e.g.* source of vitamin E) along with the natural zeolite as a carrier for achieving higher delivery in the desired site accomplished [56]. Several oral medications such as metronidazole, sulfamethoxazole, and aspirin cause some severe/unfavorable stomach and intestinal problems. Hence, there is a need for carriers to transit these drugs from the upper digestive system and reduce their side effects. In this regard, natural zeolites such as clinoptilolite were used as antacid material with maintaining their structure in strong acidic pH; moreover, in the case of use, they do not modify the medical effects of other drugs [57].

For some reason recently focuses have been concentrated on the drug response *via* normal zeolites; various types of drug placement inside the cavities and achievement of a sustainable drug release from zeolites. In terms of interacting force between drug-zeolite, drug trapped in the porosity, zeolite provide a very weak hydrogen bond to the drug to deliver it in the targeted tissue and not being detached easily [58,59]. Conducted clinical and pharmacological studies in 2015 approved that zeolites don't cause any biological damage to humans [25]. They have been used as a raw material in the pharmaceutical industry in various forms of drug carriers. Absorption of drugs by the natural clinoptilolite matrix was demonstrated the delivery of the prescribed amount rate could slow down, as well as reduce the side effects of these drugs [60]. Clinoptilolite-based medicines can also be useable for children in the form of chocolates, sweets, and biscuits to make them more edible. Furthermore, in the gastrointestinal tract, the crystalline zeolite X and A at a lower pH (*i.e.* lower than the pH of the stomach) were used for Ketoprofen release [61]. Decontamination of tetracycline polluted water through treating with β-zeolite [62] showed that 90% of tetracycline adsorbed onto β-zeolite just within 20 min which followed by a relatively slow process. The β-zeolite adsorption capacity was increased while pH was increased from 4.0 to 5.0, and with a further increment of pH, adsorption capacity lightened. So, as it can be deduced from the previous example, pH dependency of tetracycline adsorption in terms of the β-zeolite surface-charge-changes would result in a different profile of adsorption. Aluminum atoms in the zeolite played a crucial role in the uptake; the adsorption increased with the increasing aluminum content in the zeolite. The spectroscopy study showed that the spectra of tetracycline changed upon the interaction with zeolite beta, which could be ascribed to the formation of complexes of tetracycline and aluminum atoms in the zeolite surface. Nuclear magnetic resonance and UV–Visible spectroscopy studies decipher Al atom's participation in the tetracycline adsorption. Moreover, Fourier transforms infrared spectroscopy provided insight into the tetracycline amino group complex-forming role with the zeolite surface. In a parallel study, carbonated–nitrated type zeolite (Can(AlMg)) was synthesized in that zeolite X was applied for their aluminum and silicon sources. Synthesized material represented antacids properties and carbonated–nitrated cancrinite-type zeolites were very efficient in comparison with Al-Mg metals based antacids. A possible interaction between the carbonated–nitrated cancrinite-type zeolite and the tetracycline molecule in acid solutions was investigated and results showed that a possible interaction among tetracycline molecules and their synthesized antacids in the stomach like conditions. Despite these results, simultaneous administration of both drugs (antacids and antibiotics) wasn't efficient and it has been recommended that to take the cancrinite–zeolite 1 h before administering the tetracycline [63]. In contrast, another study was showed that the simultaneous use of drugs and ion increased the desired performance, to this aim, sulfadiazine and silver ion were loaded into β-zeolite to enhance the anti-bacterial property. In a similar study done by the same researchers, focused on zeolite Y carrier with sulfadiazine and silver ions [64]. Interestingly, silver introduced in forms of solid-state (*i.e.* Ag0/Ag2O nanoparticles) and ion exchange (*i.e.* Ag + cations) encapsulated in a mesh-like structure of zeolite Y.

The method of subsequent SD loading does not influence its release kinetics when the H-form of the zeolite is used as a carrier and no noticeably sustained release can be achieved compared to pure SD. The amount of deposited SD, the nature of its interaction with the carrier as well as the release kinetics is influenced, however, by the presence of silver. These characteristics depend also on the SD loading procedure performed in solid-state or in liquid. When SD is loaded in solution, a part of the

zeolite silver ions is released and interact with SD, forming AgSD and restricting the bioavailability of the formulation. By solid-state SD deposition, the reaction between the drug and the silver is limited within the limits of inter-atomic interaction, and total but prolonged drug release occurs, compared to the unmodified zeolite. Thus, perspective drug release systems for topical use in burn injury can be easily prepared by the latter procedure of solid-state SD encapsulation into Ag-modified zeolite Y.
In regards to recruiting external simulations, in 2016, a research group through an electrical field, controlled folic acid (FA) release which loaded into Y zeolite/chitosan hydrogel in that drug loading went through the ion exchange process [65]. In a molecular interaction level, the Si/Al ratio in conjugation with cross-linking ratio (*i.e.* mesh size-promoting effect) determined the amount of FA release. Hence, a combination of the inorganic with polysaccharide biopolymers like zeolite/hydrogel opens up new windows for the potentiality of drug matrix in the beneficiary of prolonged drug release *via* electrical stimuli without drug diffusion before the application time.
Uglea *et al* synthesized and analyzed the effects of CuX zeolite in combination with cyclophosphamide. The obtained data illustrated that the severity of the anticancer effect of zeolite-cyclophosphamide was similar to that of cyclophosphamide, while zeolite with cyclophosphamide preserves the concentration range of 100–1000 ng/ml plasma of this drug in the blood, and it can be supposed that zeolites function as a sustained release controller of the drug [66].
Besides, researchers in 2014 encapsulated Ibuprofen and Indomethacin inside X and Y zeolites for observing their anti-inflammatory effect, and follow up their release at different pH in gastric and intestinal simulator solutions and it was revealed that these two zeolites had a positive effect on drug release and higher anti-inflammation effect [67]. Later, the implementation of the natural zeolite carrier for delivering ibuprofen went through the physical absorption at three levels of (10, 20, 30 mmol/100 g) concentration of cationic surfactants, benzalkonium chloride, and cetyl pyridinium chloride, in buffer solution at pH = 7.4 was studied. Based on the amount of zeolite mass used and surfactant type (which modifies the surface of the zeolite) drug sorption undergoes different affection. Sustainable release of ibuprofen was achieved during 8 h with a 40% release and based on adsorption/partition model, overall hydrophilic/hydrophobic interactions of the ionizable drug with modified surfactant/zeolite composites surfaces [68]. Although, recruiting vinylidene fluoride-tetrafluoroethylene polymer with Y-zeolite for evaluation of ibuprofen release rate resulted that drug release was dependent on the magnitude of zeolite amount [69].
In 2016, the removal of Cephalexin from aqueous solution, assessed with the aid of natural zeolite and magnetic Fe_3O_4 nanoparticles coated on natural zeolite [70]. By manipulating favorable changes at the zeolite surface, the various drugs can be loaded into pores; the desired rate of release can be achieved in the targeted site.
In magnetic drug delivery, faujasite zeolite used as a crust to protect the metal core together with doxorubicin, which made it easy to prepare and prevent the accumulation of magnetic nanoparticles [71]. In another study, the percentage of loading of gentamicin antibiotic on ZSM-5 and hydroxyapatite biomaterials revealed that the percentage of drug loading in ZSM-5 was approximately four times in comparing with loading in HA, and the release of drug in ZSM-5 was more appropriate and continuous and might this advantage originates from the high surface area of zeolites per gram so that the area for ZSM-5 zeolite is 380 m^2/g and for the hydroxyapatite, it is 8.1 m^2/g [10]. In 2013, Tavolaro *et al* demonstrated that zeolites with MFI and MOR structure for some reason account for good absorbent

features, especially for gastric ulcer drugs. A porous state of zeolite crystallinity provides suitable thermodynamic stability in the biological medium, which preserves the drug against gastric acid [72]. Even earlier in 2011 investigations had been done by Fatouros and et al. showed the effects of the salbutamol and theophylline drugs which used to treat asthma disease, in BEA-structured zeolites like beta zeolites and the result supported that salbutamol penetrates more and more into the structure of the BEA rather than theophylline [73]. Chloroquine is one of the most powerful anti-malarial drugs; a pertinent study to achieve sustainable release, zeolite P used for this purpose, according to their result, zeolite P with cationic surfactant increased the absorption of chloroquine more than the condition without cationic surfactant, while X-zeolite without surfactant had no drug absorption [74].
In recent years, many studies have been focused on the loading and evaluation of a 5-fluorouracil inside the zeolites in which that is one of the important anti-cancer drug [75]. Encapsulation of this drug with two zeolites with the BEA structure related to synthetic β-zeolite, and NaX-FAU zeolite related to FAU zeolite with both different porosity and structure. By comparing 5-fluorouracil the loading capacity, FAU zeolite loaded more than the BEA zeolite, which this result was in agreement with dynamic simulations. The whole 5-fluorouracil drug is released over 10 min from NaX-FAU zeolite while for the BEA in a multi-stage and a longer period drug released. The survival of Caco-2 cells in the NaX-FAU sample is lower than the BEA sample, which confirms better biocompatibility of BEA zeolite [76]. Furthermore, 5-fluorouracil loaded into zeolite Y was suggested alternative platform for releasing profile, so they found that releasing rate in the laboratory environment during the first 10 min was 80–90%, which implies the suitability of Y zeolite for carrying and releasing 5-fluorouracil anti-cancer drug [77]. 5-fluorouracil loading and release profile in different types of ZSM-5 (Na-ZSM-5 & H-ZSM-5) zeolites were argued that releasing the rate of ZSM-5 samples in body's simulant fluid were 84–93% [78]. Another anticancer drug in which encapsulated into Faujasite and A zeolites was Hydroxycinnamic acid (CHC) and evaluation of human colon carcinoma cells (HCT-15) survival for Faujasite and A zeolites displayed the good biocompatibility. However, CHC/Zeolite induced cell death was higher than that of CHC, which indicates zeolite instinct potential for drug loading and transfer them to cancer cells [79]. Later this idea generated that zeolites could show toxicity effect in cancerous cells *via* loaded drugs, and studies put more attention on tracking the clinoptilolite zeolite effect on the development of several cancer models *in vitro* and *in vivo*. Results revealed that clinoptilolite could act as an anti-cancer agent. Clinoptilolite is orally ingested in several mice and dogs that have different tumors and ultimately lead to improvements in the animal's health and quality of life [80].

3.2. Zeolites for detection of biomarkers and construction of biosensors

Zeolites are favorable resources for constructing biosensors, and also systems for collecting and sensing biomarkers of serious diseases, mainly tumors. In biosensing, clinoptilolite and β-zeolite are capable of developing potentiometric biosensors based on co-immobilization of enzymes with different types of zeolite which went through pH-ion-sensitive field-effect transistors [81].
So far, different types of zeolites have been applied for the development of enzyme-based electrochemical biosensors. Zeolites were added to the biorecognition components of the biosensors and served as additional elements of the biomembranes or adsorbents for enzymes.

Since the detection of urea is of great concern in biomedical and clinical analysis application, attempts to develop a zeolite combined polymeric membrane biosensor (clinoptilolite) were successful. For this, a urea biosensor has been organized by covalent biding of urease directly to the surface of an ammonium-sensitive field-effect transistor (FET) [82].
Being a temporarily essential amino acid for humans, L-arginine is necessary for children in the growth phase and under some pathological conditions in adults. For that reason, the observation of arginine-based therapeutic medications within body fluids as well as the control of their quality is of vital importance. So, L-arginine conductometric biosensors were developed based on arginase and urease cross-linked by glutaraldehyde in a single selective membrane and modified with clinoptilolite. The clinoptilolite intrinsic properties helpful for the conductometric detection of L-arginine [83].
The determination of DA is an issue of great importance for investigating its physiological functions and identifying nervous diseases resulting from unusual DA metabolisms such as epilepsy, senile dementia, schizophrenia, Parkinsonism, and HIV infection. Zeolite-modified electrodes (ZMEs) from a subsection of the so-called "chemically modified electrodes " (CMEs) have been significantly investigated and promoted by Murray and co-workers. Specifically, considerable efforts have been dedicated to the improvement of voltammetric biosensors based on ZMEs. A novel chemically altered electrode is constructed based on an iron (III) fixed zeolite modified carbon paste electrode (Fe3 + Y/ZCME). The electrode was evaluated as a sensor for the sub-micromolar determination of tryptophan (Trp) and dopamine (DA) [84].
The use of organophosphate insecticides has produced severe difficulties in the environment, human health, and ecosystem. Therefore, the monitoring of these pesticides is very essential. Researchers have improved biosensors for easy, online, and rapid monitoring of organophosphate pesticides. Polyanilinenanocrystalline zeolite-based acetylcholinesterase biosensor was used to detect pesticides with higher activity compared to conventional polyaniline [85].
Recently, glucose biosensor based on *Escherichia coli* has been improved. Regardless of some problems, such as the activity of glucose dehydrogenase (GDH) and the lower electrode stability, application of zeolite in biosensors can increase the enzyme activity, while the use of glutaraldehyde (GA) as a cross-link can develop the electrode stability.
The progress of new fabrication methods of organized nanoparticles on surfaces is important for electronic, optoelectronic, biological, and sensing applications. Usually, chemical alteration of SiO2 substrates with silanization techniques are used for possible biosensor and electronic applications where the targeted biological components are assembled onto modified substrates. By the aid of electron beam lithography (EBL), it is possible to form decorations of zeolite nanoparticles on SiO2 with microfabrication techniques. For this purpose, three different assembly techniques were tested. These techniques include spin-coating (SC), ultrasound aided strong agitation (US), and manual assembly methods [86].
The Human Immunodeficiency Virus (HIV) is a deadly virus that infects many people worldwide. Recently, Zeolitic imidazolate framework-based biosensor was constructed for the detection of HIV-1 DNA. ZIF-8 one of the zeolitic imidazolate frameworks as quenching platforms for the detection of HIV-1 DNA, which was recognized to be effective for highly sensitive detection of HIV-1 DNA [87].
Newly, a paper chip was developed using zeolite nanoflakes and graphene oxide nanocrystals (Zeo–GO) for electroanalysis of ketamine [88].

A polyaniline–zeolite nanocomposite material was fabricated for the sensitive detection of the neurotransmitter acetylcholine and the subsequent biosensor was further applied for the detection of toxic organophosphate pesticides [89].
Also, Zeolitic imidazolate frameworks (ZIFs) was applied as the matrix for constructing integrated dehydrogenase-based electrochemical biosensors for *in vivo* measurement of neurochemicals, such as glucose [90].
Alpha-fetoprotein (AFP) is the single standard serum indicator for the detection of hepatocellular carcinoma (HCC). Hence, it is necessary for initial diagnosis, curative effect assessment, therapeutic prognosis checking, and longstanding survival appraisal from HCC cancers. So, silver enclosing EMT zeolite nanoparticles (NPs) were constructed by ion exchange and further applied in Alpha-fetoprotein (AFP) detection. The silver-containing EMT based immunosensors shows great performance in AFP detection, which well recompenses the conductivity and surface area [91].

3.3. Wound healing

Another important application of zeolite, which has been created curiosity over the past two years belongs to the use of these ceramic biomaterials to control bleeding and wound healing. Because of its porous structure (including micro and macro channels), zeolites have a high absorbance capacity of environmental liquids and also the potential of intrinsic negative surface charge helps to prevent bleeding. Narsh Ahuya *et al* reported that the use of zeolite hemostat can control hemorrhage and dramatically reduce mortality from a lethal groin wound. Modifications of zeolite hemostat can decrease the exothermic reaction and attenuate tissue damage. In 2012, the hemostatic performance of natural zeolite granules (NZG) was evaluated and compared with Quickclot in a lethal rabbit model of a complex groin injury. Accordingly, both of the studies dealt with NZG and Quikclot groups achieved 100% clotting efficiency. Also, a good healing property was achieved in all animals that survived in the NZG group, while three-quarters of the animals in the Quikclot group developed serious necrotic tissue. So this study briefly indicated that the application of NZG in the lethal rabbit model of groin injury significantly decreased the mortality and accelerated the wound healing process. Moreover, their low cost, easy manufacturing process, and high bio-compatibility make them an excellent alternative for synthetic zeolite-type hemostatic products. Another study by Jing Li in 2013 demonstrated that Zeolite releases Ca2+ into blood, thus accelerating the intrinsic pathway of blood coagulation and shortening the clot formation time. In detail, *via* a cation exchange reaction (*i.e.* ion exchange process) zeolite release Ca^{2+} and absorbed Na^{+} and K^{+} upon contact with the blood. Increment in Ca^{2+} concentration consequently shortened both the APTT and clot formation time *in vitro*. Cation exchange is an important mechanism of action underlying the hemostatic effect of zeolite. The simplified illustration presented in Fig. 3.

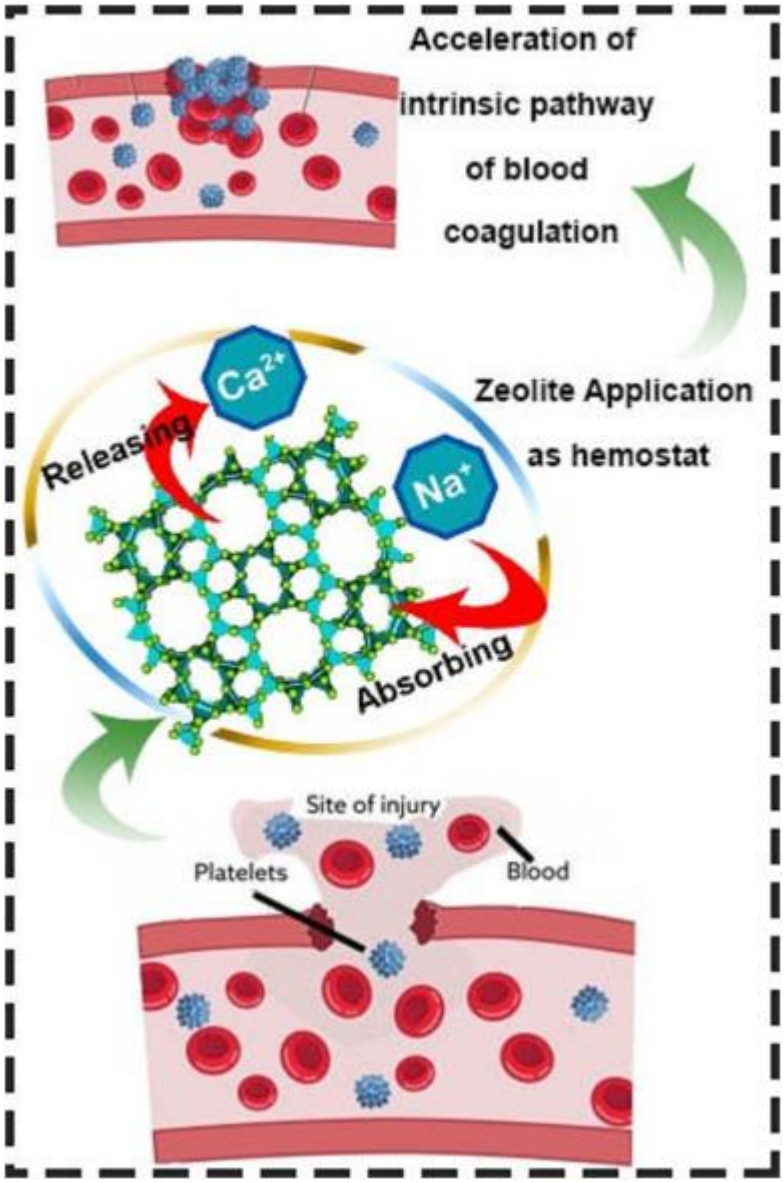

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Fig. 3. In the case of blood vessel injury, the departure part undergoes the intrinsic pathway of blood coagulation, meanwhile, the application of zeolite as a hemostat causes faster and facilitated coagulation of the blood. Because zeolite could release Ca^{2+} and absorbed Na^{+} and K^{+} upon contact with the blood.

In 2014, prepared gelatinous scaffolds with varying degrees of Faujasite zeolite for healing wounds purpose. According to this research, a 0.5% zeolite scaffold with gelatin has been chosen as the optimum scaffold, which has a cavity size of 10–350 μm. Confocal microscopy images illustrated that by increasing the amount of zeolite in gelatin, the death rate of bacteria increases; in fact scaffold rises oxygen content which is available for cells and causes the highest survival rate of NIH3T3 fibroblast cells among the samples. *In vivo* studies on rats showed that the ulcers produced in the skin were regenerated after 20 days [[92], [93], [94]]. Another study done by Drexel by Michelle and colleagues, in 2014, made a mixture of zeolite A and nitric oxide to prepare ointment for wound healing usage. Based on *in vivo* tests result, it determined that after 20 days of non-zeolite ointment application, 85% of the wound was healed while zeolite and nitric oxide ointment showed that 95% of

wound healed within the same period. Therefore, zeolite and nitric oxide can be used as an anti-bacterial drug that improves wound healing [95,96].

3.4. Scaffolds used in tissue engineering

Finding the probability that materials like zeolites in tissue engineering scaffolds worth it or not, have been tested by a dozen of researchers (Table 2); approaches have made up with the idea that inquiring for its potential applications in regenerative medicine due to biocompatibility and cation exchange character. Abdul Kadir and et al. synthesized hydroxyapatite (HA) and zeolite-Y bioactive composites with microwave-assisted wet precipitation method. The formation of dense tissue layers based on simulated body fluid (SBF) assay suggests that silica-based material provides a better condition for normal human osteoblast cells in terms of supporting and proliferation aspects. The viability assay of the cells revealed the best Zeo–HA samples for cell toxicity consideration in which this ratio increased cell proliferation about 2.3 times was higher than the case-control group [97].

Table 2. Zeolite based nanocomposites and their biological effects.

Used materials	Synthesis method	Used cells	Outcomes	Ref.
Zeolite + silver ions	3D printing	MC3T3-E1 cells	-Excellent mechanical properties -Inducing the formation of apatite -Antibacterial activity against *S. aureus* and *E. coli*	
Zeolite + PCL-PEG-PCL	Electrospinning	Human dental pulp stem cells (hDPSCs)	Better support of proliferation, adhesion and osteogenic differentiation of hDPSCs	[140]
Zeolite + PLGA	Electrospinning	MG63 osteosarcoma cell line	- Improved mechanical properties - PLGA/zeolite electrospun fibers was recommended for bone tissue engineering	[98]
PVA/collagen + Zeolite + Silica nanoparticles+	Electrospinning	Chondrocytes isolated from articular cartilage of white new Zealand rabbits	Cell proliferations on the PVA/collagen/nZe and PVA/collagen/nSi were strikingly higher than on the pure PVA/collagen	[99]
Fluorinated porous zeolite particles (FZ) + polycarbonate urethane (PCU)	Solvent casting and particulate leaching method	Human coronary artery smooth muscle cell (HCASMC)	HCASMC proliferation on PCU-FZ scaffolds was significantly greater than on control scaffolds. Surprisingly, cell infiltration depths on the PCU-FZ scaffolds was double that on PCU control scaffolds	[100]

Used materials	Synthesis method	Used cells	Outcomes	Ref.
Clinoptilolite (CLN)/PCL–PEG–PCL	Reproducible solvent-free powder compression/particulate leaching technique	Human fetal osteoblasts (hFOBs)	- The presence of CLN improve mechanical properties and *in vitro* protein adsorption capacity of the scaffold - Higher osteoinductivity in terms of enhanced ALP, OSP activities and intracellular calcium deposition for CLN/PCL–PEG–PCL scaffolds - Increasing CLN content triggered faster CaP precipitation on the composite scaffolds	[101]
Hydroxyapatite (HA) + zeolite-Y	Microwave-assisted wet precipitation method	Normal human osteoblast (NHOst) cells	Nano-structured zeolite–HA composites had good bioactivity and *in vitro* cell compatibility thus can be considered as a potential candidate for bone tissue engineering applications	[141]
Pure zeolite membranes formed from synthetic crystals (MOR, FAU BEA, MEL & MFI)	Hydrothermal methods	Primary human fetal fibroblasts (cell line GPE 86, ISTGE),	Zeolite membrane were very stable in aqueous media (apart from ionic strength and pH values), able to adsorb pollutant species and to confine undesired toxic ions (present in culture media).	[104]
Zeolite MFI + Ti6Al4V(titanium alloy)	Hydrothermal synthesis methods	hFOBs	Zeolite MFI-coated titanium alloy was shown to facilitate osteoblast adhesion, induced osteointegration and promoted the differentiation of hFOBs into mature osteoblasts compared to bare titanium alloy	[142]

In 2017, nanocomposite Poly lactic-*co*-glycolic acid/zeolite scaffolds synthesized by Davarpanah Jazi and et al. in which any kind of zeolite beads on the fibers didn't observe. They adapted the electrospinning method and poly lactic-*co*-glycolic acid with nanocrystalline zeolite merged with 3, 7, and 10 (wt%). SBF's result presented an appropriate amount of apatite crystals formation on the scaffold surface regarding that mechanical property of scaffold improved which accounts for the zeolite nanocrystals presence. MG63 osteosarcoma cell line seeded on the scaffolds and PLGA/zeolite 7 (wt%) MTT assay was the best proportion in terms of biocompatibility concepts during the 1, 4, and 7 days after cultivation. SEM images provided that after

7th-day MG63 cells started to penetrate to fibers hollow space, which is an implication of cell immigrations. So satisfying the interconnected porous structure, improved mechanical properties, apatite generation, good biodegradability, and cell compatibility all are compelling reasons for why we should develop zeolite-based material in the bone tissue engineering field [98].
In 2016, Mehrsa and *et al* synthesis a scaffold *via* polyvinyl alcohol (PVA) - collagen with zeolite and silica nanoparticles by electrospinning technique for articular cartilage application. In this study, it has been assumed that silica material increased mechanical features, osteogenicity, bioactivity, and activation of Ca^{+2} dependent Wnt5 signaling pathway; for zeolite increasing of polymer stiffness. MTT assay revealed that in terms of the proliferation rate of chondrocyte cells on PVA/Col/nZe and PVA/Col/nSi after four days increased and promoted attachment of chondrocyte cells. In the end, SEM images showed the difference between cell attachments for both PVA/Col/nZe and PVA/Col/nSi but it showed the cytocompatibility and facilitated cell spreading on the surface of the scaffolds [99].
One of the hurdles in the tissue engineering field is that available oxygen molecules aren't sufficient at the inner part of the designed scaffold and lack of the oxygen cause cell death or surface cell assemble, so different strategies had been implemented about this issue like dissolved oxygen in the culture medium, but reported novel approach in 2011, enhanced delivered oxygen to the Human coronary artery smooth muscle cell (HCASMC) which immigrated to the inner part of the 3D scaffold. They created an oxygen vector embedded in fluorinated zeolite particles within three-dimensional (3-D) polyurethane scaffolds. First of all, they reacted 1H,1H,2H,2H perfluorodecyltriethoxysilane with zeolites particles, and then new fluorinated-zeolite (FZ) crystals mixed into 3-D polyurethane scaffolds so FZ-containing polyurethane (PCU-FZ) obtained. With considering the viability and proliferation of HCASMC on polycarbonate urethane (PCU scaffolds without FZ particles) and scaffolds that contained non-fluorinated zeolite particles, and PCU-FZ revealed cell numbers especially on PCU-FZ scaffolds after 4 and 7 days increased meaningfully in comparison with other control groups; in addition to that PCU-FZ did not induce toxicity for all days (Fig. 4). So they successfully synthesized fluorinated zeolites that delivering more oxygen to cells without toxicity [100].

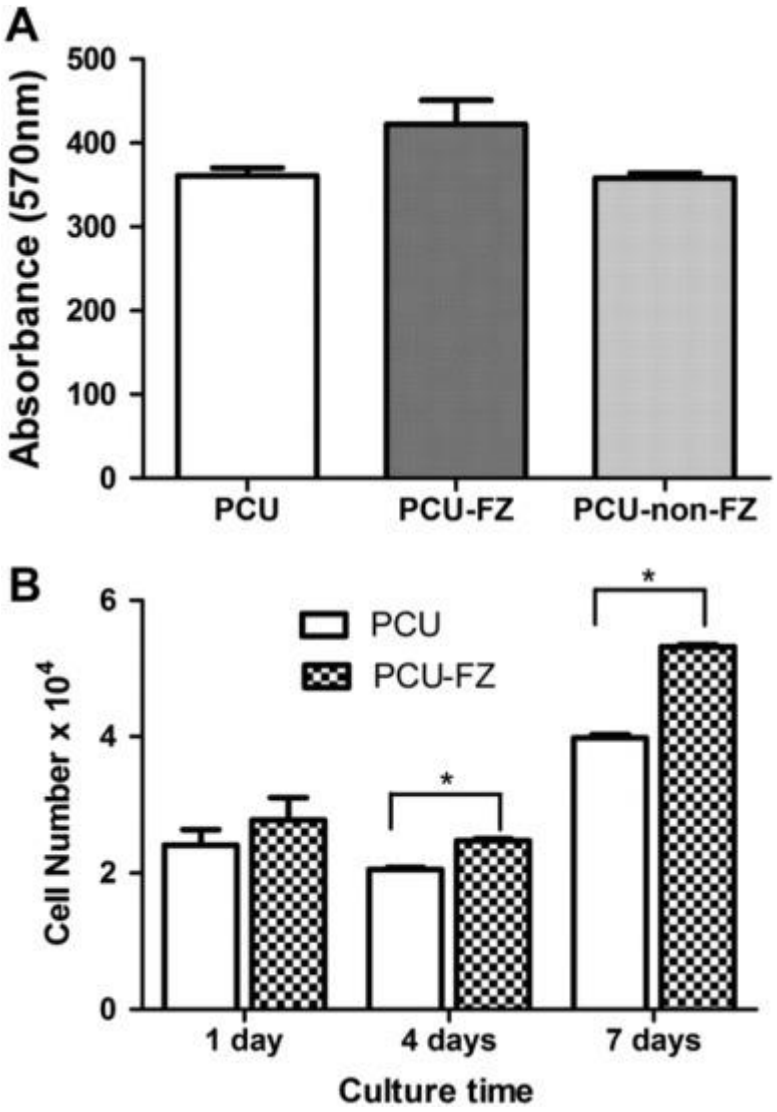

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Fig. 4. Human Coronary Artery Smooth Muscle Cells (HCASMC) (A) viability and (B) growth on PCU, PCU-FZ, and PCU-non-FZ 3-D scaffolds. Data are means ± SD for experiments conducted in triplicate. *Statistical significance. Reproduced with permission, Elsevier [100].

Human fetal osteoblast cells seeded on the composite clinoptilolite/poly(e-caprolactone) poly(ethylene glycol)-poly(e-caprolactone) by Pazarceviren and *et al* with clinoptilolite contents (10% and 20%) within the polymeric matrix through solvent-free powder compression/particulate leaching technique. Following pursuing observation convinced them that this scaffold offers a beacon of hope for enhancement of bone regeneration in bone tissue engineering applications. To shed more light on, scaffolds proved that they can increase intracellular calcium deposition, alkaline phosphatase, and Osteopontin activity [101].

Zeolites are considered as bio-ceramic materials, and bio-ceramics are also used as bone tissue engineering scaffolds with similar bone tissue properties. In 2014, for preparing bone scaffolds, they combined Y zeolite in various weight percentages with hydroxyapatite, and with the MTT assay, they showed that the survival rate of cells in the scaffold containing 10% zeolite was better than the rest of the weight percentages [97]. According to a study conducted by Banu *et al* at the University of Texas in 2012,

zeolites can prevent osteoclast activity and osteoporosis [102,103]. In 2016, Tavalaro *et al* researched the biomedical applications of zeolite-based scaffolds, and the results showed that zeolite due to easy preparation and reusability, biocompatibility, easy sterility, stability in aqueous media, and the ability to absorb contamination and unpleasant toxic ions, have led to cell development, and also this scaffold is economically and anti-bacterially suitable for the culture medium. By culturing human embryonic fibroblasts on the BEA, MOR, FAU, MEL and MFI structures, it was shown that after 6 days of culture, the number of cells on the zeolite surface was higher in the MOR, BEA, FAU, MFI and MEL structures, respectively. Also, the survival rate of cells in the zeolite with an MFI structure is more than the rest of the structures [104]. American researchers at the University of California also showed that zeolites generally increase osteoinductivity, osteoconductivity, and osteointegration in bone tissue engineering [105]. Other good features of zeolite in the application of that in bone scaffolds include an increase in growth and differentiation of osteoblast cells [19], an increase in the production of TGFβ in osteoblast, osteoconduction [105], an increase in the amount of mRNA associated with TGFβ, and also an increase in its release [106]. Regarding these results, zeolite is an important material that widely used in tissue engineering particularly bone tissue engineering.

3.5. Anti-bacterial and anti-microbial

Bacterial resistance to antibiotics nowadays becoming a global concern in the treatment of diseases, so biocompatible materials and various medicinal plants are considered as ancillary treatments along with the removal of bacterial agents. Generally, zeolites have an anti-bacterial effect and have been used with other complementary elements that enhancing their antimicrobial properties [17,107]. To achieving this goal, researchers in 2015 ionized zeolite Y with sodium, copper, zinc, and silver for comparison of their antibacterial level and used two indicators in this regard, so *E*-coli bacteria and *Saccharomyces cerevisiae* yeast had chosen. According to these tests, the materials provided had good antibacterial properties, but the pair of Zn/Ag element showed superior antibacterial properties. The sequence of their antibacterial activities were Zn0.05Ag-Y > AgZn0.05-Y > AgCu-Y = CuAg-Y > Zn0.05Cu-Y = CuZn0.05-Y = NaY [[108], [109], [110], [111]]. By loading antibiotic drugs inside zeolites, the antibacterial effect of the drug can be increased, so that the antibacterial effect of the gentamicin with ZSM-5 zeolite is approximately four times higher than that of gentamicin with hydroxyapatite alone. Hence, the amount of bacterial growth in that type of zeolite is lower [10]. Zhou *et al* applied zeolite with silver to increase the antibacterial properties of dental materials. 365.73 mg of loaded silver per g of zeolite showed that minimum inhibition concentrations for *Escherichia coli* and *Staphylococcus aureus* were 1 and 3.5, respectively. Also, the minimum bactericidal concentrations were 3.5 and 5, respectively [[112], [113], [114], [115], [116]].

3.6. Implant coating

Zeolites plus silver ions have attracted the attention of researchers for implant coating propose because of their biocompatibility, anti-adhesive properties, easy in construction on some types of surfaces, complex geometry, and reasonable prices. In 2011, a thin layer of zeolite with a thickness of 1–4 μm was covered on titanium alloy surface in conjugation with silver ions considered in terms of antibacterial and

anti-adhesive properties. Moreover, in another sample to increase the anti-bacterial effect, because silver ions made the surfaces high hydrophilicity and represented some antibacterial and antifouling properties. In this regard, different proportions of silver ions were incorporated into zeolite and were coated onto the surface of the titanium section. Two pieces with zeolite exhibited good biocompatibility in toxicity tests, and in the case of the silver-containing coating were advantages (Fig. 5). This study proved that zeolite coating on titanium piece in conjugation with anti-bacterial inducing ions is an alternative application that can be used in orthopedic and dental implants [117].

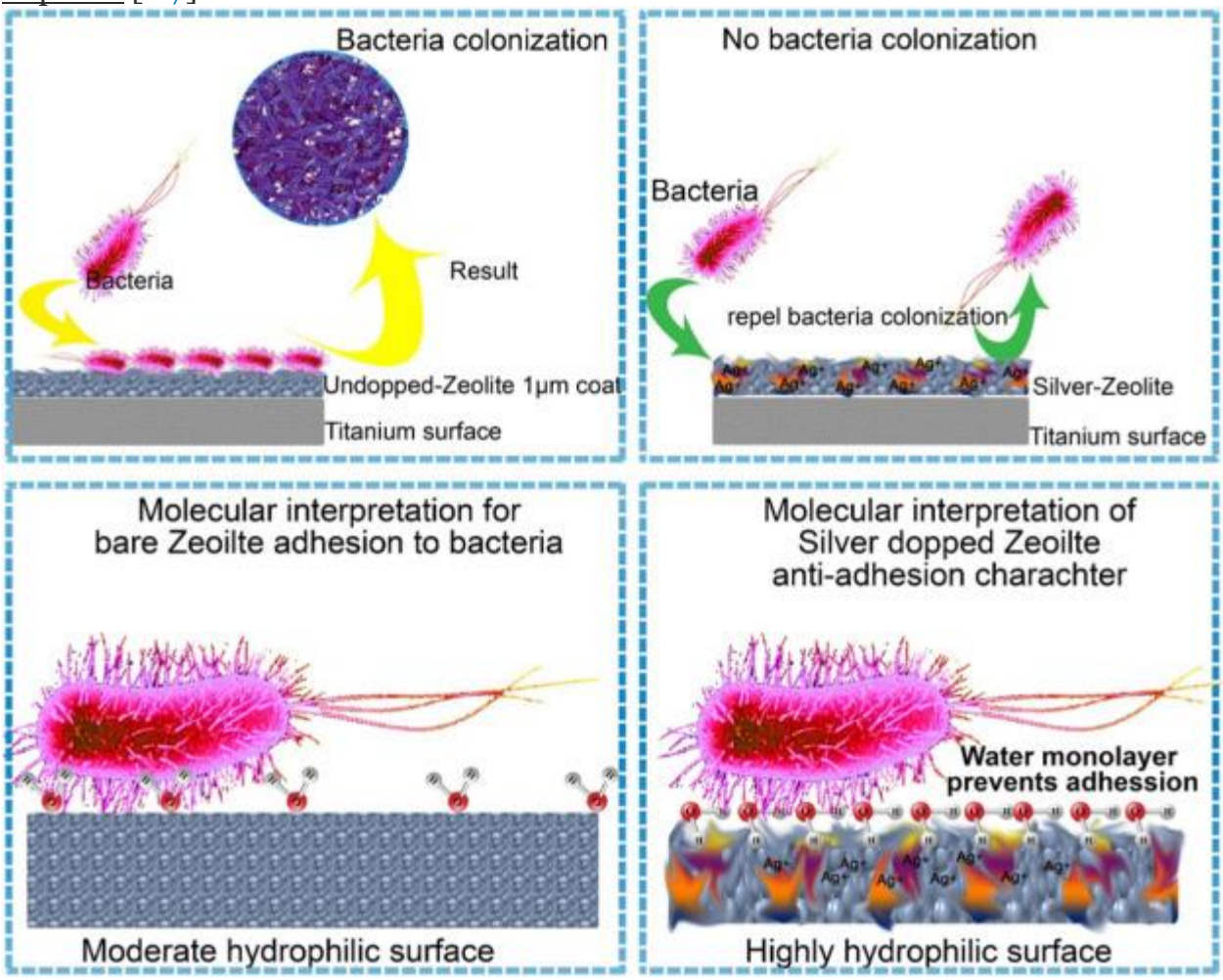

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Fig. 5. Simplified representation of A) bacteria adhesion and colonized bacteria on the pure Zeolite coatings, B) molecular reasons for bacteria adhesion interpret illustrate that low surface energy (*i.e.* hydrophobic surface) interact with biomolecules, cells or bacteria through electrostatic or van der Waals force directly. C) Through doping silver ions in Zeolite structure, hydrophilicity increases as well, and in the case of D) high surface energy (*i.e.* higher hydrophilic), the surface cannot provide a firm anchor for bacteria because of the H2O monolayer and water molecules associates slipping of the bacteria from the surface which is called antibacterial and antifouling properties.

A resistant coating should have a high hardness and low elastic modulus, and coatings for dental usage must hold on the aforementioned factors. In a study, assessment of chromium, cadmium, zeolite, and 4130 steel materials, it has been

revealed that zeolite after chromium with the hardness of 12.1 had a hardness of 6.3, while the elastic modulus of zeolite was lower than the other three materials. The unique balance between high hardness and low elasticity modulus results in considerable flexibility that prevents cracking during bending and rotation. In terms of constituting material and structural aspect, high crystallinity of zeolite that establishes by strong covalent bonds between constituent elements gives a reason for the high rigidity of this material; although, porosity accounts for its low elastic modulus. By compared zeolite with the other three materials (*i.e.* chromium, cadmium, and 4130 steel), zeolite coatings were more resistant to corrosion and hardening against abrasion, so it was a preferable substitute for these materials for electroplating [118]. Yong Li et al. in 2015 used zeolite with MFI structure for covering the titanium pieces' surface. In this regard, the titanium section was polished well and cleaned with distilled water and ethanol and placed in the ZSM-5 solution to form zeolite nuclei crystals on the piece. Then, by performing *in vivo* studies on rabbits, it observed that in the implanted group that were covered by zeolite, the rate bone and implants connection were visible, and newly generated bone tissue was more than that of non-zeolite-coated implants [105,119]. Researchers later than put forward the increasing antibacterial properties hypothesis and in this context zeolite doped with silver and zinc elements and then coated surfaces. They get to conclude that to enhance antibacterial properties in their research [120,121]. The coating of titanium components with zeolites, in addition to improving their performance, also reduces their price and also prevents the release of toxic ions such as aluminum and vanadium [18]. The results of Hang chau *et al* in 2014 showed that, in addition to a coating of titanium pieces, zeolite can also be used for coating steel fibers too [122].

3.7. Contrast agent

Material porosity in combination with their surface engineering ability is an important factor in the realm of MRI imaging with multimodal functionality, although zeolite nanoplatforms in conjugation with magnetic, radioactive, or optical agents are one of the eminent candidates. For promoting the safety profile and elongated circulating time, a higher amount of surface PEGylation (*i.e.* mushroom regime) for nanozeolite LTL which embedded through ion-exchanging with paramagnetic GdIII ions showed remarkable longitudinal relaxivity. On the other hand, higher PEGylation causes (*i.e.* brush regime) puts more barrier on the proton/water diffusion and exchange between the interior part of zeolite and unfavorable effect on relaxivity. This research illustrated that the optimized amount of PEGylation could increase the relaxivity and also preventing Gd ions leakage for considering as a promising probe for MRI applications [123].
In this part, several examples in which bolded in their recent advances and promises argued as well. Platas-Iglesias *et al* loaded gadolinium (Gd) on NaY and NaA zeolites and studied to improve the resolution of MRI imaging. They introduced effective factors such as dealumination, porosity, and calcification for loading gadolinium on zeolite. So that sketching novel porous substances that have high relaxivities as a contrast material in MRI, some important properties must be considered. The material must be able to retain gadolinium ions inside the framework and gadolinium strongly coordinated to the framework to ensure a longitudinal relaxivity and to the diffuse water molecules from the inside of the substance to the bulk water, the size of pores should be large sufficient. Through preparing gadolinium suspension with 1.3–5.4% at different temperatures showed that the relaxation rate was significantly

increased by reducing gadolinium loading [[124], [125], [126]]. In another study, gadolinium/zeolite was used as an oral contrast agent to increase the resolution of MRI images in the digestive tract. The compound was prepared as a suspension and given as a feed to the dog and evaluated before and after the MRI. By examining the vital signs in the blood and urine of the dogs, Gd absorption and toxicity were evaluated in that no Gd uptake and toxicity were found in the blood and urine of the dogs. So gadolinium/zeolite can be a promising contrast medium to increase the resolution of MRI images in the digestive tract [127]. These results show that the use of zeolite (as an MRI contrast agent) in various ways can be important in enhancing the quality and resolution of MRI images.

3.8. Harmful ions removal from the body

Porous materials commonly used as metal ion (*i.e.* mercury, arsenic, and cadmium) adsorbents because they have a high surface area. These elements are the facilitators and accelerators of some cancers and heart disease. So, by eliminating a significant proportion of those elements in internal circulating blood, the risk of cancer probably decreases. In 2014, chitosan-zeolite combination with different proportions to absorb harmful elements such as copper and lead, supported this idea that biomaterial adsorption depends on the concentration of metal ions, contact time, and the ratio of zeolite to chitosan; also it was found that 1:1 ratio has the highest porosity and absorption of metal ions. The highest copper ion absorption was approximately 89% of total concentration, while for lead ion it was approximately 60%. The absorption rate in different concentrations was also investigated and it revealed that with an increase in concentrations, the amount of absorption increased and in the concentration of 150 mg/l, the highest absorption was obtained [59].

3.9. Hemodialysis

In the artificial kidneys field, zeolites appeared as potential hemodialysis fluid filters. The ability of zeolite selective absorption is due to its crystalline state and the manipulation of structure, which is connected by channels and holes with distinct and uniform size. Molecules that have appropriate dimensions/size hold on with the canals or holes given character as a result molecule can be inserted in supposing holes and the surface absorption at the internal hole can occur. In a study, Japanese scientists have succeeded to separate urea, acid ureic, p-cresol, creatinine, and indoxyl sulfate from hemodialysis fluid in the dialysis wheel system, zeolites recruitment. In this way, the hemodialysis fluid is re-usable and improved up to 10% rather than the conventional hemodialysis. In this research, a mixture of zeolite with polymer was used to remove uremic toxins for blood purification in patients with renal failure. Nanofiber with EVOA polymer (ethylene-*co*-vinyl alcohol) employed to create the initial matrix of polymer and β-zeolite with a 37% Si/Al ratio to absorb uremic toxins, such as creatinine. SEM images pointed out that more than 90% of zeolites in this solution are inside nanofiber [128]. Schaf et al. (2005–2012) conducted a variety of studies in France to remove uremic toxins through the application of zeolites with the structure of MFI and MOR, as a result, 75% creatinine with MOR zeolite and 60% PICs with MFI zeolite has been removed from initial concentrations which it was better than conventional dialysis systems with the elimination of 67% creatinine and 29% p-cresol. These results indicate that zeolite potentially can eliminate renal uremic toxins without direct binding to the serum albumin [[129], [130], [131], [132]].

3.10. Teeth root filling

Zeolite is of interest to dentists due to their antibacterial properties thereby researchers have been inquiring for recruiting zeolite-based material to fill tooth root. However superior esthetic aspects of all-ceramic dental prostheses are inevitable, for this reason, in an independent study it was concentrated on improving opacity and the fracture resistance of alumina and zirconia-toughened alumina (ZTA) frameworks. In this research, two types of materials sodalite zeolite-infiltrated alumina and sodalite zeolite-infiltrated ZTA were synthesized in front of the control groups were glass infiltrated alumina (IA-glass) and glass-infiltrated ZTA (IZ-glass). Fracture toughness and elastic modulus revealed that IZ-SOD and IA-glass occupied the highest among the groups in that appropriate brightness makes them suitable for anterior teeth restorations.
In vitro studies, in considering antibacterial behavior through additive materials, it has investigated the inhibitory effect of Glass Ionomer Cements (GICs) containing 2% w/w of silver-zeolite on *Staphylococcus aureus*, Streptococcus milleri, and *Enterococcus faecalis* bacteria that are common in dental filling after 24 and 48-h by agar incubation. Most bacterial growth inhibition observed for *Enterococcus faecalis* bacteria. The results of this study revealed that GIC has an inhibitory effect on the growth of three bacteria and that the addition of silver-zeolite increases its antibacterial effect proportional to its concentration [133,134].

3.11. Safe side or danger side: adapting zeolite materials on the human body

In the biomedical field might each one of the single atoms in a different form and different shape have been adapted for various purposes, from diagnosis to treatment levels. In this context, to expand zeolite potential related applications have been endeavored to obtain the best version of the conjugated form of non-toxicity and biocompatibility. For various types of zeolites, it has been argued that *in vitro* cytotoxicity evaluation was depending on surface chemistry, shape, through manipulation of point of zero charge, dimensions, and dosage. In other words, by looking at Si/Al ratio in the zeolite framework, the alterable basic/acidic nature of these materials can be modified by doping different metals into the crystalline framework. Changeable acid-base (pH-triggered [135]) characteristics subsequently not only alter selective adsorption affinities but also influence hydrophobic-hydrophilic properties and this means adjustability in controlling the cytotoxicity [136]. So one of the important issues at controlling cell death (toxicity) is pertinent with doping metals into zeolites structure which moderate H^+ ions concentration and also the charge of the particles [137]. In general, it can be said that functionalization with organic compounds additives with providing better cell adhesion feature make the zeolite more potent for adsorption of blood content. For example, zeolite-loaded chitosan composites represented synergistic involvements for hemostatic activity and functionalization with hydrogel bead composition caused neglectable cytotoxicity of zeolite particles *in vitro* [138]. In another interesting research, adhesion and growth of fibroblasts on the pure structure of zeolite membranes have been figured out. It's been concluded that surface of Mordenite, Zeolite Y, Zeolite β, Silicalite-2, Silicalite-1, and V-Silicalite-1 zeolite membranes when presented to fibroblast cultures, the nanocrystals nonflat and jagged surfaces stimulate the cells to extend more filopodia to form focal adhesion points with the substrate and also reaching to inter-grown zeolite membranes underneath as possible [104]. In other research, in terms of cell adhesion and proliferation, nano-hydroxyapatite reinforced zeolite

composites *via* MTT assay for human osteoblasts (NHOst) onto the disc surface was much higher than the control [139]. These few examples somehow show that toxicity can be tailored through engineering the composition and surface moieties through polymers. However, it seems that here it has been needed more researches to be done for concluding more evidenced results.

4. Conclusion and future prospective

Zeolites are nutritious, antibacterial, biocompatible, non-toxic, highly absorbent substances that expanding the use of this biomaterial in various fields of medical science. Therefore, a suitable choice of either synthetic or natural zeolites in conjugation with polymers is important for use in drug delivery systems, wound healing, tissue engineering scaffolds, coating of implants, hemodialysis, gas absorption and removal of harmful ions from the body. Zeolite is categorized based on the applications, biological properties, physical and chemical properties that can help researchers who are interested in exploiting zeolite to select the appropriate zeolite. The present study illustrated that the most highlighted application of zeolite in medical sciences is in drug delivery systems and absorption and release of several drugs such as anticancer drugs have been studied. In conclusion, the application of zeolite in biomedical sciences is in expansion and is expected to grow in the coming decades on account of the development of innovative zeolite-based delivery systems along with the emergence of new classes of therapeutics that require smart delivery systems for their biological activity.

Declaration of competing interest

The authors declare that they have no competing interests.

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