Emerging Multimodel Zirconia Nanosystems for High-Performance Biomedical Applications

Garima Rathee, Gaurav Bartwal, Jyotsna Rathee, Yogendra Kumar Mishra, Ajeet Kaushik,* and Pratima R. Solanki*

Advancement in nanotechnology supports system development to achieve rapid, affordable, and intelligent health management and has raised the urgent demand to explore multimodel affordable metal oxide nanostructures with the features of biocompatible tunable performance and scaled-up processing. Keeping this as a motivation, zirconia nanostructures (Zr-NSs) are emerging as nanostructures of choice for advanced biomedical applications due to affordable, scalable production, easy surface modifications, tunable surface morphology, multiphase stability, and acceptability by biological features such as biocompatibility, viability for bioactives, and a high isoelectric point of 9.5. Zr-NSs, alone and in the form of hybrids, and nanocomposites have demonstrated notable high performance to develop next-generation biosensors, implanted materials, and bioelectronics. However, their excellent salient features toward high-performance biomedical system development are not well articulated in the form of a review. To overcome this knowledge gap, herein an attempt is made to summarize state-of-the-art Zr-NS preparation techniques as per targeted applications, surface functionalization of Zr-NSs to achieve desired properties, and applications of Zr-NSs in the field of biomedicine for health wellness. The challenges, possible solutions, and authors’ viewpoints considering prospects in mind are also part of this report.

1. Emergence of Zirconia Nanostructures (Zr-NSs)

In recent years, the unprecedented emergence of nanotechnology with ever-augmenting technological advancements in the overall characteristics of nanosized particles has fascinated umpteen scientists across the globe. Its prominence mostly boomed with multifarious utilization in almost every scientific ground, including manufacturing, technology, and medicine. More precisely, nanostructured metal oxides play a vital role in numerous areas of biotechnology and biomedical science attributed to their unique palette of superior mechanical, electronic, and pharmacological properties.[1–7] The elements comprising metallic characteristics have shown the immense potential of creating mixed oxides by various synthesis methods. Due to their exclusive electronic configuration, the transition metal oxides exhibit strong electronic transitions, wide bandgaps, high dielectric constants, and excellent electrical characteristics.[8] These metal oxides regulate metallic, insulator, or semiconductor features of the material and, in turn, display tunable optical, magnetic, electric, mechanical, thermal, catalytic, photochemical, and optoelectronic properties.[9] Due to such exemplary features of the transition metal oxides, this area has seen an upsurge in substantial biomedical research and is still a subject of deep stimulating investigations. A myriad of research groups are dedicated to the fabrication of metal oxide NSs with exclusive sizes, shapes, and properties to explore the miraculous yet hidden opportunities in this field.
Out of established mixed metal nanostructures, Zr-NSs have emerged as an illustrious mode for countless applications attributed to the superior properties of zirconia such as very high wear resistance, fracture toughness, chemical inertness, superb mechanical strength, less thermal conductivity, biocompatibility, and greater ionic conductivity. Such stupendous characteristics of zirconia permit speckled applications in ceramics, fuel cells, secondary battery materials, chemical sensors, biosensors, gas sensors, alkaline and lithium-ion batteries, solar cells, piezoelectrics, pyroelectrics, actuators, magnetics, ferroelectrics, corrosion applications, optical devices, waveguides, lasers, superconductivity, magnetoresistance, supercapacitors, and so on. Figure 1 schematically displays the multifaceted utilization of Zr-NSs in diverse domains of science. Although numerous investigations have been done to discover the prospective zirconia nanosystems’ applications, the field still has a lot of future opportunities to offer, as evidenced by the continuous surge in the number of published articles in the modern era (Figure 2).

Herein, we will explore the high-performance advanced biomedical applications of surface-functionalized multimodel biocompatible Zr-NSs synthesized using appropriate and optimized chemical routes. Apart from the biomedical performance of high demand, a critical and careful analysis was performed on up-to-date investigated synthesis methods. Such informative analysis provides a clear idea about selecting an appropriate design and developing Zn-NSs of desired properties in Zr-NSs needed for industrial application. Further, this Review also highlights the fundamental challenges associated with state-of-the-art Zr-NSs to develop next-generation implanted systems, diagnostics tools, therapeutics, and tissue engineering where an affordable, scalable, biocompatible, and sustainable Zr-NS is the critical requirement. The outcomes of this Review will serve as one of the best platforms to fill the knowledge among multidisciplinary experts aiming to design Zr-NS-based research related to the field of next-generation biomedical sciences.

2. Zirconia: An Overview

Zirconium (40Zr), also known as “ceramic steel,” is a transitional metal element with an electronic configuration [Kr] 4d^2s^2. It is named after the mineral “zircon,” which is the major source of zirconium. Naturally, it does not exist in pure form and found

Figure 1. Schematic illustration of state-of-the-art applications of Zr-NSs.
extensively in the combination.\cite{11,13} It is also found as free oxide zirconia (ZrO₂) in the mineral baddeleyite.\cite{19} The native forms of minerals contain a substantial amount of elemental or radioactive impurities. Therefore, they cannot be used as the primary source for a biomedical purpose.\cite{10,22,23} The presence of these impurities alters the material properties effectively, even at minute concentrations. Several time-consuming and complex procedures are needed to effectively separate these impurities and the generation of pure zirconia powders. These pure powdery forms could later be used for biomedical applications.

It is well studied that ZrO₂ crystals can assume three crystallographic symmetries: monoclinic (m), tetragonal (t), and the cubic (c) symmetry.\cite{24} The modification in the crystallographic patterns of pure zirconia entirely depends on the temperature and pressure applied. The monoclinic polymorph (m), the most stable form at standard conditions, is stable up to 1170 °C. This form is primarily found in all-natural deposits. With rise in temperature, the monoclinic structure converts into the tetragonal (t) polymorph at 1170 °C with a slight contraction of \( \approx 4\% \) in overall volume. The tetragonal form undergoes further shrinkage in volume at a very high temperature and finally transitions into the least usable cubic (c) symmetry at 2370 °C.\cite{22,25} Generally, volume shrinkage is less commonly observed in ceramics at higher temperatures, and therefore, such unconventional properties of zirconia allowed chemists to unfold its vast biomedical applications. Moreover, these lattice transformations are found to be reversible. Upon cooling, tetragonal or cubic symmetry reverts to the monoclinic form. The \( t \rightarrow m \) transformation begins at 950 °C with a substantial increase in volume (\( \approx 4.5\% \)), making the lattice more rigid and hard.\cite{13,26} Furthermore, the inability to accommodate this expansion promotes internal stresses in the lattice, which leads to catastrophic failure, crack propagation, and ultimately results in prosthesis failure.

Doping of pure zirconia with relatively low quantities of several dissolvable metallic oxides, such as MgO, CaO, CeO₂, Y₂O₃, and La₂O₃, results in the lowering of the phase transformation temperature. This substantially reduces the strained phase, i.e., monoclinic phase, and stabilizes the tetragonal as well as cubic phases at room temperature.\cite{24,27} By doping such stabilizing oxides, different types of zirconia ceramic nanomaterials have been introduced for numerous applications. These primarily include yttrium-stabilized tetragonal zirconia polycrystals (3Y-TZP)\cite{9,28} glass-infiltrated zirconia-toughened alumina (ZTA)\cite{29,30} ceria-stabilized zirconia (12Ce-TZP),\cite{31} magnesia partially stabilized zirconia (Mg-PSZ),\cite{32} zirconia-containing lithium silicate ceramics (ZLS),\cite{33} etc. We will discuss this in more detail in Section 5.

3. Investigated Synthesis Techniques for Zr-NSs: Careful Analysis and Recent Developments

The exceptional properties of zirconia with innumerable uses are the consequences of constant advancement in the designing techniques of Zr-NSs. These progressions are planned in such a manner that the required properties of the target materials such as shape, size, morphology, and crystallinity could be achieved efficaciously. Several techniques have been implemented to fabricate nanomaterials that can be primarily categorized into two basic approaches: the “bottom-up” and “top-down” approaches.\cite{34} The former approach is established on the construction of a nanometric structure from below, i.e., from the level of single atoms or molecules that condense with each other in solution or in the gas phase to generate a nanosized material, whereas the latter approach includes grinding or milling of a micrometer structure into very small portions of up to nanometer size. The synthesis techniques in the liquid and gaseous phases are placed in the “bottom-up” approach, whereas solid-state routes are categorized in the “top-down” approach. The “bottom-up” approach provides many more advantages and is therefore frequently used for the synthesis of nanostructures. In this section, we will discuss the various techniques used for the fabrication of Zr-NSs.

3.1. Liquid-Phase Methods for Zr-NS Preparation

Liquid-phase methods include “bottom-up” manufacturing approaches such as coprecipitation, hydrothermal, sol–gel, solvo-thermal, emulsion precipitation, hydrolysis, microwave-assisted, and electrochemical deposition (Figure 3).

3.1.1. Coprecipitation Method for Zr-NS Preparation

The coprecipitation process is a facile, conventional, and perhaps the most straightforward approach to synthesizing various pure/multinary nanocrystals. It is mainly preferred for the synthesis of oxide-, fluoride-, oxo-hydroxide-, or oxyfluoride-functionalized nanocrystals. This standard synthesis approach typically includes dissolution of a salt precursor (generally in the form of chloride, nitrate, acetate, or oxychloride) in an aqueous solution followed by the precipitation of corresponding hydroxides by the dropwise addition of precipitating agents such as NaOH or NH₄OH. The precipitate is then separated and purified by washing it multiple times with distilled water. After that, it is dried in a hot-air oven. This method allows the generation of particles with diverse diameters based on the nature of reaction substrates and experimental conditions. It is a cost-effective process, easily applicable on a larger scale for commercial applications while requiring minimum effort. It permits the generation of nanomaterials in good to excellent yields through an eco-friendly pathway. It avoids the involvement of hazardous organic reagents and solvents, thus mitigating the harmful effects on the environment. By controlling a series of experimental conditions, the process also allows precise control over structural characteristics of synthesized NSs.

To date, the coprecipitation method has been frequently used for the generation of Zr-NSs by various research groups for varied applications. For instance, Zhou et al. successfully fabricated nonagglomerated, crystalline, and nanosized Al₂O₃-ZrO₂, with 7 nm as particle diameter (Figure 4).\cite{35} Hsu et al. used this method for designing tetragonal zirconia polycrystals stabilized by yttrium (3 mol%), with 21.3 nm as diameter.\cite{36} Furthermore, Lan and co-workers\cite{37} synthesized CdO₂-ZrO₂, lead-based catalysts, in a single phase with particle diameter (5.2–28.9 nm). The foremost benefit of this technique is the probability of attaining the material in quantities consisting of grams\cite{38} and the capability of using easier and cheaper nanoparticle precursors and equipment.\cite{39} However, this method suffers from the disadvantage of incapability of controlling the size of the final NS. To
control the agglomeration of the nanoparticles, a direct precipitation method was suggested by Wang et al.[39] for the synthesis of nano-ZrO$_2$ using ethanol as a solvent instead of water.

### 3.1.2. Sol–Gel Method for Zr-NS Preparation

Another well-known process extensively used for the fabrication of Zr-NSs and nanocomposites is the sol–gel method, a wet-chemical route entailing multiple steps of specific physical and chemical processes such as hydrolysis, sol formation, gelation, drying, dehydration, and densification. This processing technique is primarily associated with the preparation of a sol, followed by gelation and solvent removal.[40] In this method, the solution (sol) gradually progresses toward constructing a gelatinous network comprising both liquid and solid phases, which further transforms into a solid crystalline or amorphous structure. The translation of the sol into a gel form primarily depends on the dehydrated colloidal solution generated from the material hydroxide particles. Generally, the alkoxides of different elements are used as starting precursors in the sol–gel method.[46] The initial step involves the hydrolysis of precursors (metal–organic compounds) into oxohydroxide compounds, followed by the condensation step resulting in a metal hydroxide network. Finally, the polymerization step provides a porous gel. After that, heating and drying of the porous gel provide the required nanostructures.

In 2017, Abd Ellateif and Mitra reported the sol–gel method for designing zirconia-enclosing hydrophobic silica nanoparticles (NPs).[41] The characterization studies exposed the difference in textural and structural properties of silica–zirconia nanomaterials from those of pure silica, mainly dependent on the zirconium percentage in the materials. Bashir et al. synthesized ZrO$_2$–ZnO NPs using the sol–gel process and reported that NPs were of small sizes after doping zirconia with zinc oxide.[42] Other materials designed by the sol-gel method are ZrO$_2$–CrO$_2$,[43] ZrO$_2$–TiO$_2$,[44] and ZrO$_2$–GO.[45] Akkari et al.[46] designed nanocrystalline sulfated ZrO$_2$ over mesoporous silica using a sol–gel technique. In this study, zirconium acetylacetonate and tetraethyl orthosilicate were used as reaction precursors, and in situ H$_2$SO$_4$ was used for the sulfation reaction.

The sol–gel method is the most advantageous method for synthesizing complex metal oxides, temperature-dependent organic–inorganic hybrid materials, and the production of ceramic and glassy materials of superior purity and homogeneity.[35,36,47,48] The method requires a lower process temperature than other gas-phase methods. It executes multiple advantages such as fewer instrumentation costs, generation of nanostructures with stable and high surface area, no release of toxic wastes, and the ability to attain color layers.[40]

### 3.1.3. Hydrothermal Method for Zr-NS Preparation

The hydrothermal method is an example of solvothermal methods in which nanomaterials are fabricated by dispersing the reaction precursors into the appropriate solvent and further exposing the solutions to relatively high-temperature and pressure conditions. When the solvent used for the dispersal of the initial precursors is water, the method is called the “hydrothermal method.” It is a wet-chemical technique comprising several synthetic procedures such as hydrothermal crystallization,
hydrothermal decomposition, hydrothermal precipitation, microwave hydrothermal fabrication, and hydrothermal oxidation ultrasound-assisted hydrothermal synthesis under supercritical conditions. It involves a crystallization process in an aqueous medium under increased pressure and temperature (water’s critical point). For hydrothermal synthesis, an autoclave is generally used. Optimizing the chemical parameters (composition, concentration, type of the reactants, solvent ratio, and reducing agents) and thermodynamics parameters (pressure, temperature, and exposure time), a variety of NPs of superior structural characteristics have been synthesized over the years using the hydrothermal method.

This method has been used to fabricate all three crystalline forms of ZrO2 (monoclinic, tetragonal, and cubic forms). Moreover, based on the experimental conditions and the nature of precursors, appreciable changes have been observed in the diameters of the synthesized Zr-NPs. Caillot et al. evaluated the impact of metal reactants over the surface area of a Zr-NS and showed that the introduction of lanthanum, cerium, and titanium significantly enhanced the surface area.
of the Zr-NS (Figure 4C). However, the observed surge was not like the increase in the proportion of every metal oxide in the final product. The major advantages spotlighted by this route are the ability to conduct the process at lower temperatures, no requirement of any kind of thermal exposure at high temperatures, excellent quality and purity of the obtained nanostructures, and controllable grain shapes. The rise in the nucleation could also be monitored by altering the hydrolysis temperature, increasing the hydrolysis time, introducing surfactants, and fluctuating the pH.[49] However, the hydrothermal process also suffers from various detriments such as apparatus intricacy, expensive setup, and the incompleteness to direct the procedure’s observations.

3.1.4. Solvothermal Method for Zr-NS Preparation

Various organic solvents have been used as alternatives to water during the solvothermal process. Such designing strategies are imperative for the fabrication of nanostructures with notable crystalline characteristics. During the solvothermal process, a chemical reaction occurs in a sealed vessel (e.g., autoclave or bomb) at a temperature significantly higher than the solvent’s boiling temperature. Such conditions intensify the aptitude of solvents to dissolve the precursors and accelerate the reactions between the solids. The foremost benefit of the solvothermal process is that nearly all the materials could be made soluble in the solvent by raising the temperature and pressure up to the critical point.

Exploiting this method, Liu et al. successfully synthesized ZrO2 nanostructures, i.e., nanorods, nanosheets, and linked nanosheets.[53] The precursors used for the synthesis were ZrOCl₂·8H₂O and [Zr₆O₁₄(OH)₆(H₂O)₆]₄(Cly)₆.12Cl₂H₂O (CP-2) in the presence and absence of Tween-80, Triton X-100, and sodium dodecyl sulfate (SDS). The solvothermal process was for 24 h at 200 °C. Research studies concluded the generation of single-phased monoclinic Zr-NS (Figure 4D). Furthermore, Anandan et al.[54] successfully designed ionic-surfactant-assisted Zr-NSs with 7.09–15.22 nm as the crystallite size using the solvothermal method. Detailed characterization of the nanostructures confirmed the formation of the spherical, needle-like, and cauliflower-petal morphologies. The nanostructures designed by this technique resulted in perfect crystallinity and high purity.

3.1.5. Emulsion Precipitation Method for Zr-NS Preparation

The emulsion precipitation technique is another successful liquid-phase method for the fabrication of Zr-NSs. The nanomaterials acquired by this route execute uniform dispersion and size distribution. The quintessence of this method includes the mixing of two microemulsions, which contain multiple reagents in drops. During the mixing process, these liquid drops collide with each other and interchange the reagents. In this method, one of the emulsions consists of a precipitating agent to induce precipitation on stirring. It is generally used for controlled hydroxide formation and water elimination and avoids aggregation by using precise incorporation of surface-active agents.

Using the emulsion precipitation method, Woudenberg et al.[55] designed nonagglomerated spherical Zr-NSs with a particle size of 5–8 nm. These emulsion-derived nanostructures were amorphous and tended to crystallize into a tetragonal form at 500 °C, and they were stable up to 1000 °C. Furthermore, Chandra et al.[56] reported a single emulsion-assisted direct precipitation route to fabricate tetragonal Zr-NSs via an isooctane/AOT/water system. It was found that ZR-NSs of different crystalline symmetries could be generated depending upon the molar ratio of water and surfactant. The results inferred that the pure tetragonal phase was observed at lower water: surfactant molar ratio (Rw); a mixture of tetragonal and monoclinic phases was obtained at intermediate Rw, and pure monoclinic phase was observed at higher Rw. The emulsion precipitation method provides a multipurpose procedure for the fabrication of Zr-NSs. Such a method offers the aptitude of controlling the geometry, size, homogeneity, morphology, and surface. Also, a complicated and expensive equipment is needed during the process.

3.1.6. Hydrolysis Method for Zr-NS Preparation

This route of fabrication of Zr-NSs is centered on the hydrolysis of precursors. For synthesizing nanostructures via the hydrolysis method, zirconia compounds and urea are primarily dissolved in deionized water or ethanol. Further, these solutions are boiled continuously in a closed system until colloidal sol is formed. It is the boiling stage where the nucleation and crystal growth take place. The NPs formed in the colloidal solution are collected by high-speed centrifugation and washed thoroughly to remove all the impurities. In the hydrolysis method, the progress of the nanostructures is ruled by the initial concentration of the precursors and the boiling time. Like all other designing methods, the hydrolysis method also offers specific advantages, such as the generation of nonagglomerated and nanosized materials and the use of simple and cheaper equipment.[57] Numerous researchers have used the hydrolysis method for enhancing the surface area of Zr-NSs.[58–60] Inoue et al.[58] designed a novel approach for the synthesis of monoclinic Zr-NSs with high thermal stability and surface area.

3.1.7. Microwave-Assisted Method for Zr-NS Preparation

The microwave-assisted method of designing nanostructures is a complete and straightforward procedure that enables efficient and fast processing of nanomaterials with high reproducibility. Predominantly, this route of synthesis has been developed as a cost-effective tool for dissolution enhancement and reduction of particle size. Out of various microwave-assisted processing techniques, microwave irradiation has been successfully used for the generation of Zr-NSs. Microwaves, a type of electromagnetic radiation, are essential for inducing nucleation and growth of the material. Typically, microwave can interact with polar molecules, and these interactions cause vibrational and rotational motion among the molecules resulting in the production of heat inside the materials.

The significant merit of this approach is the constant exposure of the material to heat. In conventional methods, the transfer of heat is directly dependent on the heat diffusion rate (from the surface to the bulk). A direct interaction occurs between the microwaves at a specific frequency and the charged species of
materials in microwave-assisted synthesis. These interactions result in the generation of heat by microwaves either by collision or by conduction sensation. The microwave-assisted method executes various advantages such as uniform and rapid heating of materials, an energy-saving process, lesser preparation time, higher yield, cheap processing, and small particle size distribution.\[61\] Recently, Pakharukova et al.\[62\] designed nanocrystalline yttria-stabilized zirconia samples using a microwave-assisted method and evaluated the structural features of the derived nanostructures (Figure 4E). Manjunatha and Dharmaprakash\[63\] also utilized microwave-assisted technique for the fabrication of highly porous Zr-NSs.

3.1.8. Electrochemical Deposition Method to Fabricate Zr-NSs

As the name indicates, the electrochemical deposition technique is a deposition method that involves a current’s assistance for chemical deposition. The electrochemical deposition method does not require either high temperature or high pressure. This technique is cost-effective and easily portable. The most significant reason for its popularity is that this approach permits the deposition of multiple materials over the substrate.\[64\]

Numerous Zr-NSs have been introduced via the electrochemical deposition technique. For example, Lee and Smyrl\[65\] successfully synthesized regularly aligned zirconia nanotubes using a direct and straightforward electrochemical deposition technique. The nanotubes fabricated perpendicular to the zirconium substrate consist of an open-ended collection of well-aligned and continuous conformation with a hole size of 10 nm. In addition, Yu et al.\[66\] introduced another method using recordable compact disk (CD-R) gold substrate for designing material nanostructures.

3.2. Vapor-Phase Method

The fabrication of very fine particles without using grinding techniques could be successfully attained using the vapor-phase designing methods, such as physical vapor deposition, spray pyrolysis, ion beam irradiation, template-assisted method, and atomic layer deposition (Figure 5). During the vapor-phase method, the particles’ growth via gas-to-particle conversion happens due to surface reactions and vapor condensation. During the vapor condensation process, the particles’ growth occurs when vapor molecules and atoms condense over the particle surface.

3.2.1. Physical Vapor Deposition (PVD) of Zr-NSs

PVD is a vapor-phase technique for the construction of nanostructures. PVD, a vaporization coating practice, includes the transference of material at an atomic scale. This technique includes a series of steps. Initially, a physical method (gaseous plasma or high-temperature vacuum) is used for converting materials to be deposited in the vapor form. Then, the formed vapors are transported from the source to a low-pressure region to the substrate. Finally, the vapors condense over the substrate and form a thin film. The PVD technique can be employed for depositing films with thickness varying from a few nanometers (nm) to thousands of nanometers (nm).\[67\]

PVD technology includes a comprehensive series of deposition processes, such as hot-boat or electron-beam evaporation, ion plating, and reactive evaporation. PVD technology comprises methods based on the sputtering technique, either by ion beam or by plasma. Overall, this technique can be subdivided into two groups: evaporation and sputtering. As discussed previously, the evaporation method includes the formation of deposited thin films by the thermal route. In contrast, the sputtering method involves the dislodging of atoms or molecules from a solid target via the influence of gaseous ions.\[67\]

Recently, Arun Kumar et al.\[68\] used an electron beam PVD method to generate pure ZrO2 and ceria-stabilized zirconia (CSZ) thin films (Figure 6A). In this study, the deposition rates were varied to evaluate the correlation between the phase changes and mechanical properties. A mixture of m and t phases in zirconia films was obtained at higher deposition rates. In contrast, the tetragonal phase of zirconia dominated at a lower deposition rate. Moreover, the addition of cerium to ZrO2 completely stabilized the tetragonal phase, regardless of the deposition rate. The CSZ films increased the hardness fourfold compared to pure zirconia. Furthermore, Matsumoto et al.\[69\] also evaluated the impact of La2O3 doping on the temperature stability and thermal conductivity of electron-beam PVD-synthesized yttria-stabilized zirconia (YSZ) coating. The fabricated coating displayed tremendously lower thermal conductivity and high resistance to sintering.

3.2.2. Spray Pyrolysis to Fabricate Zr-NSs

The spray pyrolysis method is another successful vapor phase method for the fabrication of ZR-NSs. Spray pyrolysis is an innovative technique that entails evaporation or chemical dissociation of droplets consisting of the solute of required nanostructures. These droplets carried along by a gas leading to the generation of liquid-phased particles inside the droplets. Therefore, the spray pyrolysis technique can be considered an intermediate
route to both liquid- and gas-phase methods. Usually, a nebulizer is used to generate droplets, and the solute comprises droplets and is further inserted into the furnace’s hot zone to generate NPs. When the droplets shrink, a supersaturated solution is generated, resulting in the construction of smaller particles within the droplets. Moreover, various factors, such as the furnace’s temperature, the vapor pressures of the gases, and regulation of the nebulizer’s energy, regulate the particle sizes.

Peshev et al. used spray pyrolysis technology for the fabrication of polycrystalline Zr-NSs over silica substrates. The zirconium precursor solution was prepared in water/isopropanol solution. The deposited products were found to be amorphous. Moreover, after the heat-treatment process at temperatures of 500–700 °C, crystallized homogeneous dense cubic Zr-NSs were obtained. The m, c-ZrO2 was present when the temperature was varied in the range of 700–1000 °C.

As compared with other synthesizing techniques, spray pyrolysis technology displays various distinct advantages. The spray pyrolysis method uses simple experimental arrangements and equipment, which makes this technique a cost-effective one. Moreover, this method does not necessitate the usage of high-quality compositions and reagents. The particles’ size and morphology can be monitored by altering the fabricating conditions, flow rate, nature of additives, and concentration of precursors. Conversely, the method suffers from certain disadvantages such as the yield of the product being very low, chances of sulfide oxidation during air processing, and complications in estimating the growth temperature.

3.2.3. Ion-Beam Irradiation Technique to Fabricate Zr-NSs

The ion-beam irradiation technique is a plausible nonequilibrium way for material modification and phase generation. The ion-beam method is classified as a nonequilibrium technique. In this technique, the thermodynamic parameters, i.e., the temperature during the ion–matter interaction, nucleation at a depth of bulk, and pressure throughout the phase transformation, keep on fluctuating. Therefore, the ion-beam route could be an excellent choice for the fabrication of nanostructures. The characteristic lengths and timescales on which an individual cascade of ion–matter interactions occur are $10^{-9}$–$10^{-8}$ m and $10^{-13}$–$10^{-11}$ s, respectively. A typical rise in temperature per volume of nanometric scale is $10^4$–$10^3$ K. Therefore, a fast-quenching rate ($\approx 10^{15}$ K sec$^{-1}$) is obtained from fast mean relaxation techniques ($\approx 10^{-12}$ s per cascade). Moreover, kinetic conditions are also restricted by the short relaxation time, resulting in the amorphous phase or structurally simpler crystalline phases. The generation of nanostructures is also favored by the lengths and the timescales in the ion-beam irradiation method. Furthermore, the depth and area selectivity of the phase construction in the substrate could be achieved successfully in the ion-beam irradiation technique. Nanostructures with different depths could be fabricated by tuning the ion energy. Similarly, the area selectivity could be accomplished either using a suitable mask or aiming an ion beam.

The ion-beam irradiation method has been efficaciously used for the fabrication of Zr-NSs. Melnikaitis et al. used the ion-beam irradiation technique for designing pure ZrO$_2$, niobia (Nb$_2$O$_5$), silica-deposited zirconia (ZrO$_2$–SiO$_2$), and silica-deposited niobia (Nb$_2$O$_5$–SiO$_2$). The study stated that the designed ZrO$_2$–SiO$_2$ mixture experienced a transition into the amorphous phase from the crystalline phase when the content of glassy SiO$_2$ was increased in the mixture, therefore resulting in the augmentation of the laser-induced damage threshold (LIDT). Moreover, Lian et al. demonstrated that the ion-beam irradiation technique offers an opportunity for manipulating the crystal size, phase stability, and morphology of Zr-NSs. The group executed ion-beam irradiation over a bilayer zirconia film and witnessed a phase transformation.
from amorphous to tetragonal at room temperature. These observations suggest that under nonequilibrium conditions, the tetragonal phase is energetically more favorable than the amorphous state (thermodynamically stable).

3.2.4. Template-Assisted Techniques to Fabricate Zr-NSs

Template-assisted technology is a universal and multipurpose route for the fabrication of nanostructured materials. Numerous templates have been successfully established. Templates are generally divided into two groups, “hard” and “soft” templates. The hard templates comprise inorganic mesoporous materials, for example, zeolites, anodic aluminum oxides, carbon nanotubes, and mesoporous polymer membranes. In contrast, the soft templates comprise surfactant assemblies such as liquid crystals, monolayers, micelles, and vesicles. The successful synthesis of templates can be classified as electrochemical etching and ion-tracking etching.

Recently, Guan et al.\(^\text{[77]}\) reported a versatile template-assisted method for fabricating yolk–shell and hollow mesoporous titania and zirconium oxide spheres with constant pore channels (Figure 6B). The alkaline etching method was used for controlling the shell thicknesses and the cavity sizes, resulting in the generation of hollow mesoporous spheres with tailored shell crystallinity, surface areas, and compositions. In this study, silica-coated nanostructures, classified as “hard templates,” are used to design yolk–shell mesoporous nanostructures. Furthermore, other templates such as polymer nanospheres (PNs), mesoporous silica NPs (MSNs), carbon nanospheres (CNs), and mesoporous nanoellipsoid (MONs) can also be used in the future for such synthesis and for expanding the applications of this versatile approach.

3.2.5. Atomic Layer Deposition Techniques to Fabricate Zr-NSs

This technique is a subdivision of the chemical vapor deposition (CVD) technique. It is a thin-film deposition method that uses a series of gas-phase chemical procedures. Most of the ALD reactions generally use two precursors, which react with the material surface one at a time chronologically. In this method, a thin film is gently deposited repeatedly via exposure to separate reactants. ALD is an effective method for designing semiconductor devices and nanomaterials. The ALD method has been used for designing YSZ films.\(^\text{[78]}\) Moreover, ZrO\(_2\) was deposited over graphene nanosheets using ALD. This study revealed that the crystallinity and morphology of the deposited ZrO\(_2\) could be controlled within 150–250 °C.\(^\text{[79]}\)

4. Stabilization Mechanism of Zr-NSs: Exploring the Role of Doping Agents

The widespread implementation of Zr-NSs in the biomedical field is restricted to the fundamental issues linked with the t→m transformation. Upon cooling, the transition of a material from metastable t to m phase causes crack propagation, leading to material failure. However, this can be avoided by doping Zr-NSs with the appropriate doping agents, which help stabilize the more symmetric tetragonal or cubic phase of the target materials. After continuous research, metal oxides are the best doping agents for stabilizing the metastable tetragonal phase.\(^\text{[28,80]}\) Specifically, metal oxides of lanthanides and scandium groups have been routinely used as stabilizing additives over the years.\(^\text{[81–83]}\) However, certain underlying factors must be checked while selecting a proper dopant.\(^\text{[83–104]}\) These factors are listed as follows. 1) The first factor is the M\(^{n+}\) cation’s radius. When the radius of the cations is greater than the Zr\(^{4+}\) radius, it will positively influence stabilization. 2) The second factor is the valency of the M\(^{n+}\) cation. Based on the diverse stabilizations attained, it could be stated that more excellent stability is achieved by using multioxide systems, such as ZrO\(_2\) + M\(_2\)O\(_3\) + MO\(_2\) and ZrO\(_2\) + MgO\(_3\) + M\(_2\)O\(_3\). 3) The next factor that influences the stabilization is the number of oxygen vacancies introduced. The greater is the increment in the oxygen vacancies concentration, the more noteworthy is the m-phase stability. 4) The fourth factor is the crystal lattice’s distortion. Variation in the crystal lattice parameters might help in improving the stability. 5) The next factor is the grain size (GS). One of the essential issues correlated to zirconia stabilization is the impact on the GS throughout the sintering and during heat treatment. According to studies, the most anticipated dopants are those which hinder grain growth effectively. 6) Another factor is the impact on phase composition. The co-occurrence of the monoclinic phase with the metastable phases is undesirable, and its nucleation results in critical strains in the crystal lattice and dissimilar crystal growth. The dissimilar crystal growth is the cause of negative phase segregation and adverse stabilizer particle distribution. Hence, the dopant should be wisely selected, and an appropriate concentration and affinity must guide the dopant selection for stabilizing the β-phase. 7) Crystallinity or amorphousness of the dopant possesses an adverse influence on the stabilization as the nature of the dopant decides the mechanism behind the stabilization. 8) The impact of the type of dopant on the liquid solution formation during the sintering process also influences the stabilizing process. 9) The diffusion coefficient value (D\(_{M}\)) also affects the stability as this value influences the oxygen vacancies’ distribution, sintering duration, and phase composition. The higher the value of D\(_{M}\), the lesser is the sintering time and exposure of the metastable phase toward the elevated temperatures.

Among all the aforementioned factors, the most significant factors influencing the physicochemical properties and phase composition are the dopant radius and oxygen vacancies. Therefore, in this section of the Review, we will be discussing these two vital factors.

4.1. Effect of Ionic Radius to Improving the Performance of Zr-NSs

The ionic radius of metal cations is one of the critical factors for monitoring the martensitic transformation of zirconia and stabilizing the metastable phases.\(^\text{[85]}\) Using the lanthanide stabilizers, Naskar et al.\(^\text{[91]}\) reported that the cations’ radii exhibit a primitive influence on the GS and phase composition. Detailed comparative analyses were conducted to describe 1) the influence of ionic radii of various lanthanide metals, i.e., praseodymium, lanthanum, neodymium, gadolinium, samarium, and dysprosium, and 2) the connection between zirconium’s radius, the sintering
temperature, and the dopant’s concentration. All such dopants have a similar coordination number as Zr$^{4+}$ but have ionic radii higher than that of Zr$^{4+}$ (84 pm). These metal cations were classified into two groups: Group I consists of metals having ionic radii much larger than Zr$^{4+}$ (Nd, Pr, La) while group II includes those metals which have ionic radii comparatively similar to Zr$^{4+}$ (Dy, Gd, Sm). It was also determined that the metal cations of group I inhibited the growth of the α-phase and encouraged the γ-phase’ nucleation simultaneously. Furthermore, increasing the concentration of dopants resulted in the enhancement in GSs of group II stabilizers due to the reasonably higher number of γ-grains. Vossmeier et al.$^{[103]}$ investigated in their studies that doping of zirconia microspheres with La or Gd provided strong grain-growth-attenuating influence but failed to prevent t-to-m phase transformation arising above 850 °C. However, the addition of yttrium with lanthanum or gadolinium leads to the formation of particles with both efficient phase stabilization and attenuated grain growth. Thus, stable ceramic microspheres are acquired that are stable even at 1200 °C (Figure 7).

Furthermore, the influence of ionic radii of dopants is also linked with the shrinkage during the sintering process.$^{[97]}$ The stabilization is more effective when the dopant has high solubility because more significant is the solubility of the dopant, higher will be the stability of the β- and γ-phases. Therefore, it can be stated that the ionic radii have a significant influence on the shape of ZrO$_2$ elementary cells. Based on the outcomes from Jang et al.’s studies,$^{[105]}$ it could be stated that the elementary cell’s volume is related to the dopant’s size. When the cationic radius is smaller than the Zr$^{4+}$ radius, the fluorite structure gets destabilized due to reduced cell parameters. However, the reverse phenomenon of stabilization is observed when the cationic dopant radius is grander than 84 pm. Moreover, the cationic radii also influence the grain growth, densification, and diffusion during sintering. Metals with smaller cationic radius generate a more significant number of oxygen vacancies, due to which the diffusion coefficient also increases, therefore lowering the solidification temperature and sintering duration.

4.2. Effect of Oxygen Vacancies on Improving the Performance of Zr-NSs

The concentration of oxygen vacancies also influences the stability of metastable phases. The influence of oxygen vacancies has been repeatedly reported, but specific facts are not fully known to date.$^{[101,104]}$ The existence of oxygen vacancies within the ZrO$_2$ structure enhances the lattice stress and creates lattice distortion, further stabilizing the β- and γ-phases. Such stability is observed because the radius of O$_2$ is larger than that of the Zr$^{4+}$ ion, and at elevated temperatures, oxygen vacancies have high mobility. Furthermore, Li et al.$^{[86]}$ validated a direct connection between the elementary structure stability of ZrO$_2$ and dopant valency. Chaim et al.$^{[97]}$ claimed a noteworthy contribution of oxygen vacancies in the stabilization of metastable phases. Based on the results, it was stated that due to lesser activation energy, the vacancies display a more substantial diffusion coefficient, which therefore controls the grain growth. Such a phenomenon is also substantial for the characteristics of

![Figure 7. A,B] SEM images of La- and Ga-doped ZrO$_2$ particles at distinct dopant concentrations. Reproduced with permission.$^{[103]}$ Copyright 2016. John Wiley and Sons.
materials that are essential during mechanical treatment and heat treatment.

Another significant issue correlated to low-temperature degradation in the environment of human body fluids is the codoping or construction of multicomponent oxide structures. Li et al. in their study based on the Nb2O5-Ta2O5-YSZ codoped system stated that the phase stability was improved depending on the concentration and valency of the dopant. At lower concentrations, the authors reported destabilization of β- and γ-phases of ZrO2. However, when doping was done at higher concentrations of Nb2O5, the stability of the tetragonal phase upgraded as it would have improved with the germanium dopant. The Kröger–Vink notation could be used for describing the introduction of oxygen vacancies.

\[
2Zr^4+ + O_2^− + Y_2O_3 \rightarrow 2Y^3+ + V_0 + 2ZrO_2 \\
3O_2^− + N_2 \rightarrow 2N_0^− + 1.5O_2
\]  

where \( V_0 \) denotes the oxide vacancy concentration. This equation is valid for cations with valency like \( Y^{3+} \). The effective vacancy concentration \( V_{eff} \) defines the relationship between the vacancies and dopants. This relationship could quantify a selected phase by measuring the concentration of vacancies generated by the dopant.

\[
V_{eff} = \frac{[O_{Y2O3}]}{4} + \frac{[O_{Y2O3}]}{7} \ldots
\]

\( V_{O(Y)} \) denotes the generated vacancies by introducing \( Y_2O_3 \), and \( V_{O(Ni)} \) represents the vacancies produced by introducing nitrogen-containing compounds.

The diffusion coefficient of oxygen vacancies is higher than that of dopant cations. Therefore, due to the lower diffusion activation energy, the oxygen vacancies regulate the diffusion within the ZrO2 lattice. As the diffusion monitors the grain-growth factor, with growing GS, the martensitic transformation temperature decreases. The grain growth kinetics and diffusion could be controlled using a stabilizer with as low as possible a diffusion coefficient.

### 4.3. Zr-NS-Based Composites and Hybrid Nanostructures: Influence of Different Dopants

The conversion of the tetragonal (t) into the monoclinic (m) polymorph of zirconia is followed by an ample rise in volume (≈4.5%) upon cooling. Such a volume increase is adequate for catastrophic failure. The addition of the stabilizers in pure zirconia permits the retention of the t-phase at room temperature and consequently monitors the stress-generated transformation and gratefully arrests the crack propagation, resulting in excellent toughness. Based on the requisitions, multiple types of zirconia-containing nanocomposites and nanoalloys have been designed for numerous applications. Some of these composites are discussed subsequently.

#### 4.3.1. YSZ

When the ZrO2 structure is stabilized by doping with yttrium oxide, the produced material is entitled YSZ. Multiple phases of YSZ have been prepared using different mol% of \( Y_2O_3 \). Based on phase diagrams, it has been inferred that 2–3% of \( Y_2O_3 \) stabilized the tetragonal zirconia phase, 3.5–6 mol% of \( Y_2O_3 \) resulted in a mixture of tetragonal and cubic phase, and \( Y_2O_3 \) greater than 6 mol% stabilized the cubic phase. Furthermore, 8 mol% (or above) \( Y_2O_3 \) stabilized the cubic-fluorite structure.

The zirconia available as biomedical grade normally consists of 3 mol% \( Y_2O_3 \) as stabilizing agent (yttrium-cation-doped tetragonal zirconia polycrystals, 3Y-TZP). The yttrium (\( Y^{3+} \)) and zirconium cations (\( Zr^{4+} \)) occupy the cationic sites, and the construction of oxygen vacancies establishes electrical neutrality. The GS dramatically impacts the mechanical features of 3Y-TZP. 3Y-TZP becomes unstable and more vulnerable toward spontaneous t → m transformation when the GS is above the critical size. In contrast, a smaller GS (<1 m) is associated with a slower rate of t → m transformation. Furthermore, the t → m transformation is impossible when the GS is below 0.2 μm, resulting in reduced fracture toughness. Therefore, the sintering environment strongly influences the mechanical properties and the stability of the designed products. Longer durations and higher temperatures during the sintering process result in larger GSs.

The sintering temperature range for the designing of 3Y-TZP for soft machining of the dental restorations is 1350–1550 °C. Such a varied range of sintering temperatures influences the GS and phase stability. H.G. Scott established the 3Y-TZP phase diagram and declared the existence of some cubic ZrO2. Chevalier et al. investigated the critical effect of cubic phase on isothermal aging in 3Y-TZP ceramics. It was found that presence of cubic phase in 3Y-TZP ceramics lead to the irregular dispersal of \( Y^{3+} \) dopant ions, which in consequence, generate adverse impacts on aging resistance. The sintering of restorations manufactured via soft machining is conducted as a late step. Such a process eliminates the stress-generated t → m transformation, resulting in a surface free of monoclinic morphs, except that grading modifications are required.

However, for dental applications, sandblasting or grinding processes are not recommended by 3Y-TZP’s manufacturers, mainly to evade the transformation (t → m) and obstruct the creation of surface imperfections that might be to the detriment of long-term profits regardless of an apparent upsurge in strength because of transformation-created compressive stresses. Oppositely, restorations generated via hard machining of fully sintered 3Y-TZP blocks consist of a substantial quantity of monoclinic zirconia. This is related to lower reliability, surface microcracking, and higher vulnerability to low-temperature degradation. Certain successfully fabricated YSZ-based composite/hybrid nanostructures have been clubbed in Table 1 (entries 1–6).
Table 1. Summary of various Zr-based composite and hybrid nanostructures.

| Entry no. | Zr-NS-based composite and hybrid nanostructures | Synthesizing conditions | Conclusions | Ref. |
|-----------|-----------------------------------------------|-------------------------|-------------|-----|
| 1         | Nanocrystalline YSZ (yttria content varying from 8 to 15 mol%) | Fabricated by metal–organic CVD Processing conditions altered, especially substrate temperature Yttria content varied from 8 to 15 mol% | Average GSs (10–100 nm) was produced At varied Y₂O₃ content, cubic fluorite-type structure Kapitza resistance (temperature-dependent) calculated by grain-size-dependent thermal conductivity | [341] |
| 2         | YSZ nanofibers | Electrospinning was used for fabrication Y₂O₃ content used was 8 mol% PVP was used as polymeric component | Several inches of 1D YSZ nanofibers were designed successfully | [342] |
| 3         | YSZ NS coatings | Deposited via atmospheric plasma spraying (APS) YSZ NS with 7 wt% Y₂O₃ | Coating displayed a complex and unique microstructure made up of well-melted splats Vickers microhardness was equivalent to conventional values Indentation load greatly influenced the Vickers microhardness Improved thermal shock resistance was reported | [343] |
| 4         | Fully dense YSZ reinforced by rGO (reduced graphene oxide) composite | Fabricated via spark plasma sintering technique Short sonication method was used for exfoliation of GO in DMF/water solution | rGO addition enhanced the electrical conductivity of YSZ nanocomposite Thermal diffusivity improved by 12% after rGO addition Hardness decreased, and fracture toughness increased with the addition of rGO | [344] |
| 5         | Hydroxyapatite (HA)/30 wt% YSZ nanostructured composite | Fabricated via sol–gel technique Y₂O₃ content varied from 0 to 8 mol% (0, 3, 5, and 8) | Homogeneous and crack-free HA–YSZ was designed Crystallite size for cubic and tetragonal zirconia GS was around 44–58 and 75–85 nm for HA GS Uniform distribution of ZrO₂ particles might help generate homogeneous coatings and for hindering HA phase’s grain growth during calcination | [345] |
| 6         | YSZ/gadolinium-doped ceria (GDC) nanoislands | Successfully fabricated YSZ/GDC nanoislands over miscut substrates via self-assembly and powder-suspension-based methods Annealed for 5 h at 1100 °C | Miscut surfaces demonstrated an effective route for fabricating nanoislands | [346] |
| 7         | Nanocrystalline MSZ | Designed MSZ NPs via Pechini sol–gel method Influence of mole ratio of CA with EG and CA with TM, time, and calcination temperature on particle size was evaluated | Metastable tetragonal ZrO₂ and stable cubic MgO were formed | [347] |
| 8         | MSZ powders | MSZ powders designed by high-frequency precursor dissociation Magnesia content was varied | Smooth-surfaced spherical particles with irregular hollow aggregates were obtained With increasing content of magnesia, aggregate amount decreased, and spherical particles increased Increasing content also affected the powder properties, such as bulk density rises, and specific surface drops significantly Nanostructured zirconia was present in powders with 8.6 and 13.9 mol% of magnesia | [348] |
| Entry no. | Zr-NS-based composite and hybrid nanostructures | Synthesizing conditions | Conclusions | Ref. |
|----------|-----------------------------------------------|-------------------------|-------------|-----|
| 9        | CSZ-TBC, CSZ/micro-Al₂O₃ and CSZ/nano-Al₂O₃ TBCs | Coatings fabricated via an atmospheric plasma spray method | -Results stated that the CSZ/nano Al₂O₃ TBCs executed more remarkable thermal cycling behavior than CSZ and CSZ/micro-Al₂O₃. Failure of CSZ and CSZ/micro-Al₂O₃ was linked with thermally developed oxide and oxide stresses. | [349] |
| 10       | Nanocrystalline xCeO₂ – (1–x)ZrO₂ (x = 1, 0.75, 0.5, 0.25, and 0 in wt%) | Fabricated via chemical coprecipitation method | Samples displayed single cubic phase | [338] |
|          |                                               | pH was kept constant at 10 | Crystallite size coated samples remained similar because of the EB PVD parameters (Figure 8B) | [338] |
|          |                                               | Resultant precipitate was dried for 8 h at 353 K | Oxygen vacancy of C30Z50, C75Z25, and C100 increased significantly | [338] |
|          |                                               | The green pellet was formed via hydraulic press | CS30Z50, C75Z25, and C100 exhibited 3–4 orders improved oxidation protection than bare AISI304 | [338] |
|          |                                               | The green pellet was annealed at 1473 K | | |
| 11       | CSZ microspheres                              | An external gelation route was used | Nanostructures were confirmed by small-angle scattering method (X-ray and neutron) | [350] |
|          |                                               | ZrO₂ and CeO₂ existed in CSZ microsphere | | |
|          |                                               | CSZ microspheres produced were smooth and spherical | | |
| 12       | Nanostructured CSZ coating                    | Nanostructured CSZ coatings fabricated by the plasma-sprayed method | CSZ NS coating consisted of no molten CSZ NPs, which are incorporated into the molten CSZ NP matrix and microsized columnar CSZ grain structure CSZ NS coating consisted of fewer microcracks and pores and was denser than conventional CSZ coating The CSZ NS coating displayed greater thermal shock resistance than conventional CSZ coating and showed enhanced toughness and degraded microcracks and porosity | [351] |
|          |                                               | | | |
| 13       | Cordierite and CSZ NCs                        | Pure cordierite was designed by solvothermal method 12 mol% CSZ was fabricated by coprecipitation and gelatin technique The varied content of CSZ (0–20 wt%) was mixed with pure cordierite to fabricate sample blocks of required shapes Nanocomposite blocks were sintered at 1100–1400 °C | Results displayed that ceria acted as a stabilizer and acted as sintering assistant for cordierite establishment Ceria also enhanced the structure and compressibility of NCs All the characteristics displayed significant upgrading than previously reported data | [352] |
| 14       | CSZ (ceria 16 mol%) thin films               | Pure ZrO₂ and CSZ (CeO₂ 16 mol%) thin films were designed via the EB PVD method Variation in deposition was done (1, 4, 8 Å⁻¹) to associate the phase change with mechanical property | Characterization data indicated the existence of mixed m and t ZrO₂ phases in the films, but the t-phase dominates at a low deposition rate Moreover, the addition of ceria stabilized the t-phase of zirconia The CSZ film displayed a fourfold rise in hardness compared to zirconia due to full stabilization of the t-phase, which hampers the crack propagation The progress of CSZ coating might result in improved surface protection of components | [68] |
| Entry no. | Zr-NS-based composite and hybrid nanostructures | Synthesizing conditions | Conclusions | Ref. |
|----------|---------------------------------------------|-------------------------|-------------|-----|
| 15       | CYSZ TBCs                                   | Evaluated the hot corrosion behavior (HCB) of plasma-sprayed CYSZ TBCs | Plausible degradation mechanism was evaluated for HCB | [333] |
|          |                                             | HCB was estimated in the existence of Na$_2$SO$_4$ + V$_2$O$_5$ molten salts for 30 h at 1000°C | Molten salts penetrated through coating open pores and microcracks; and further formed YVO$_4$, CeVO$_4$ rod-like crystals, and semicubic Ce$_O_2$ crystals by interacting with ceria and yttria |       |
| 16       | CYSZ TBCs                                   | CYSZ TBCs were generated via air plasma spraying | Surface roughness was reduced significantly by laser glazing route along with the elimination of surface porosity | Tetragonal phase existed in both laser | [354] |
|          |                                             | Optimum parameters for CYSZ TBCs were obtained | Thermal insulation ability was lower of laser | Laser surface adjustment resulted in microstructural variations leading to the advancement of the resistance toward corrosion, thermal shock, and erosion of CYSZ TBCs |       |
|          |                                             | Laser surface modification was conducted for CYSZ TBCs | Based on the ban of further molten salt diffusion inside the deep layers of TBCs, a mechanism was suggested |       |
| 17       | CYSZ TBCs                                   | Plasma-sprayed CYSZ nanostructured TBCs were fabricated | The corrosive salts react with the zirconia stabilizers to yield CeVO$_4$, YVO$_4$, and Ce$_{0.75}$O$_2$Zr$_{0.25}$ as hot corrosion products | Nanostructured CYSZ displayed extraordinary resistance toward degradation | [335] |
|          |                                             | Chemical composition was zirconia, 2.5 wt% of yttria, and 25 wt% ceria | ScYSZ and CYSZ coating comprised nanozones | ScYSZ exhibited better bonding strength than CYSZ coating | [114] |
|          |                                             | HCB was evaluated in the existence of 55 wt% V$_2$O$_5$ + 45 wt% Na$_2$SO$_4$ at 1000°C for varied durations of time | ScYSZ and CYSZ coating comprised nanozones | ScYSZ exhibited better bonding strength than CYSZ coating | [114] |
| 18       | Nanostructured CYSZ and ScYSZ coatings       | Thermal insulation behavior, bonding strength, and microstructure of nanostructured 27.5% CYSZ with composition ceria (25%), yttria (2.5%), and 5.5 ScYSZ coating (composition – 5% scandia and 0.5% yttria) | ScYSZ and CYSZ coating comprised nanozones | ScYSZ exhibited better bonding strength than CYSZ coating | [356] |
|          |                                             | Thermal insulation behavior, bonding strength, and microstructure of nanostructured 27.5% CYSZ with composition ceria (25%), yttria (2.5%), and 5.5 ScYSZ coating (composition – 5% scandia and 0.5% yttria) | XRD results illustrated that both the TBCs displayed T-prime phases | XRD results illustrated that both the TBCs displayed T-prime phases |       |
|          |                                             | Thermal insulation behavior, bonding strength, and microstructure of nanostructured 27.5% CYSZ with composition ceria (25%), yttria (2.5%), and 5.5 ScYSZ coating (composition – 5% scandia and 0.5% yttria) | CYSZ displayed a higher thickness value and porosity | CYSZ displayed a higher thickness value and porosity |       |
| 19       | La$_2$O$_3$ doped CYSZ                       | 0.1–0.3 mol% La$_2$O$_3$-doped CYSZ (Ce$_O_2$ (5.5 mol%) and Y$_2$O$_3$ (1.5 mol%)) fabricated by coating route | La$_2$O$_3$ doping refined the GSs resulting in an enhancement in hardness and assisted ferroelastic domain switching | The valence state and oxygen vacancy concentrations of cerium also got affected, causing a variation in the stability of the tetragonal phase | [356] |
|          |                                             | Cold isostatic pressing (CIP) was done at 250 MPa | The valence state and oxygen vacancy concentrations of cerium also got affected, causing a variation in the stability of the tetragonal phase |       |       |
|          |                                             | Ceramics were attained after 2 h of sintering at 1600°C | The valence state and oxygen vacancy concentrations of cerium also got affected, causing a variation in the stability of the tetragonal phase |       |       |
| 20       | SYSZ nanostructure                          | Sc$_{2}$O$_3$ (10 mol%) and Y$_2$O$_3$ (1 mol%) were sintered as dense pellets | Sc$^{3+}$ does not segregate toward the surface | Sc$^{3+}$ does not segregate toward the surface | [357] |
|          |                                             | Sintering was performed at two temperatures (1300 and 1500°C), in dry and wet air | Plausible reason would be the size of Sc$^{3+}$ ion, which fits the zirconia lattice better than the Y$^{3+}$ ion does | Increased tolerance toward the sulfur of Ni-SYSZ compared to the Ni-YSZ cermets |       |
|          |                                             | Cooling/heating rate = 100°C/h | Increased tolerance toward the sulfur of Ni-SYSZ compared to the Ni-YSZ cermets | Increased tolerance toward the sulfur of Ni-SYSZ compared to the Ni-YSZ cermets |       |
| 21       | xSc$_{2}$O$_3$–1.5Y$_2$O$_3$–ZrO$_2$ (x = 4.5, 5.5, 6.5, in mol%) | xSc$_{2}$O$_3$–1.5Y$_2$O$_3$–ZrO$_2$ were designed via coprecipitation and calcination route | Results executed an increase in the hot corrosion resistance and phase stability of the SYSZ materials with the increase of Sc$_2$O$_3$ content due to increased rare earth–oxygen bond strength and enhanced prohibition effect on the penetration of vanadate | Results executed an increase in the hot corrosion resistance and phase stability of the SYSZ materials with the increase of Sc$_2$O$_3$ content due to increased rare earth–oxygen bond strength and enhanced prohibition effect on the penetration of vanadate | [358] |
YSZ TBCs. The method used for the fabrication of the YSZ TBCs was the plasma-spraying technique. According to the results, the nanostructured coating consisted of a lamellar structure comprising NPs and microcolumnar grains. In contrast, the conventional YSZ is comprised of columnar grain splats. Furthermore, Chen et al.\[115\] compared the thermal insulation capability of nanostructured and traditional YSZ coating over Ni₃Al substrates. The results showed superior thermal insulation capability for nanocoating due to bimodal microstructure consisting of semimolten particles and well-molten columnar grains having intrinsic porosity resulting from their preagglomeration (Figure 8A).

### 4.3.2. Magnesia-Stabilized Zirconia (MSZ)

Stabilization of zirconia is also successfully achieved by doping it with 15–24% magnesia (MgO). MSZ is relatively cheaper than YSZ and is generally applied in regions with lower temperature intensity, for example, exhaust jet engines’ nozzle.\[116\] MSZ nanocomposites display lower thermal conductivity than YSZ, which has been employed as a thermal coating material. Nanocrystalline MSZ has attained substantial attention because of its powerful mechanical characteristics. Based on studies, MgO–ZrO₂ nanostructures are found to have five distinct phases. These five phases are the cubic (c), monoclinic (m), tetragonal (t),

![Figure 8. SEM images of A) conventional powder (a) before and (b) after agglomeration and nanostructured powder (c) before and (d) after agglomeration. Reproduced with permission.\[115\] Copyright 2017, Elsevier B.V. B) Samples with distinct concentrations calcined at 1243 K for 24 h. Reproduced with permission.\[133\] Copyright 2017, Elsevier B.V.](image-url)
delta, and orthogonal (o) phases. A total of 4–8 and 8–12 mol% of MgO stabilize partially stabilized zirconia (PSZ), and >13 mol% of magnesia stabilizes zirconia’s cubic phase.\textsuperscript{[117]} MSZ nanocomposites are very useful at a higher temperature (>500°C) due to the higher transformation-toughening mechanism. The t-transformation takes place over 900°C, which makes MSZ nanocomposites beneficial for high-temperature applications. The sentence appropriately conveys its intended meaning. Systematic doping and temperature treatment could be used for tailoring the mechanical and structural properties of MSZ nanocomposites. In addition, prolonged high-temperature exposure would cause volatilization of stabilizers, eventually resulting in the destabilization of the Zr-NS. In MSZ, magnesia evaporates when the temperature is greater than 2000°C. Therefore, volatilization plays an important role in practically operating temperatures.\textsuperscript{[118]}

The creation of MSZ nanocomposites requires high temperatures with longer durations. Therefore, many methods have been proposed to prepare MSZ nanocomposites, such as coprecipitation, sol–gel, a plasma-spraying method, and alkoxide sol–gel method. MSZ nanocomposites were fabricated by the coprecipitated oxalate gel method and successfully characterized.\textsuperscript{[119]} A decrease in surface area of a MSZ nanocomposite with a rise in temperature was reported. The designed nanocomposites were peptized, and surface areas were estimated. The surface areas of these composites were lower than alcohol-washed powders due to alcohols' interaction with the surface of powders. The MSZ-based composites/hybrid nanostructures are reported in Table 1 (entries 7 and 8).

### 4.3.3. Calcia-Stabilized Zirconia (CaSZ)

Doping of zirconia with calcia (CaO) is also a successful route for achieving the stability of zirconia. CaSZ displays poor stability regarding spraying parameters.\textsuperscript{[120]} In addition, CaSZ-TBC materials also illustrate lower thermal shock resistance compared to YSZ TBC. No study has been reported about the fabrication of CaSZ nanocomposites for TBC applications. Nevertheless, CaSZ with calcia content 10–15 wt% has executed impressive applications in fuel cells. Nanospherical CaSZ (nanopowder) with 15 mol% CaO content was fabricated via the spray pyrolysis method.\textsuperscript{[121]} The spray pyrolysis method provides a single-step, time-saving, and energy-saving route for designing CaSZ nanopowders compared to traditional methods. The nanostructures obtained were mostly solid, spherical, and had a narrow size distribution. The average particle size of CaSZ NPs was between 40 and 350 nm with controlled furnace temperature, solution concentration, precipitator’s voltage, and carrier gas flow. TEM results displayed that the crystalline CaSZ particles were organized by minor crystallites, with sizes varying from 2 to 40 nm. At lower temperatures (<650°C), the nanopowders were obtained as amorphous, whereas a mixture of c + t phases was detected at higher temperatures (800°C).

Due to exceptional characteristics, partially stabilized zirconia (PSZ) has brilliantly replaced the extensive applications of fully stabilized zirconia (FSZ) in refractories and ceramic materials, mostly. Recently, Li et al.\textsuperscript{[122]} evaluated the impact of duration time and roasting temperature on calcia-PSZ stability parameters. The results exposed that a decline in the roasting duration time and temperature synchronously improved the zirconia stability rates. XRD patterns confirmed the martensitic transformation and partial conversion of cubic zirconia phase into monoclinic ZrO$_2$ phase at 1450°C for 4 h.

#### 4.3.4. CSZ

Another doping metal used to stabilize zirconia is cerium (Ce$^{4+}$), without generating oxygen vacancies. But the GS of CSZ is significantly greater than that of 3Y-TZP, mostly due to the prerequisites of high sintering temperatures and extended durations. However, CSZ appears to be a promising candidate for biomedical applications.\textsuperscript{[123,124]} Yet, published articles related to nanostructured CSZ are very limited. According to the phase diagram, CSZ exhibits a cubic, fluorite phase when x in Ce$_{1-x}$Zr$_x$O$_2$ is <0.15 and a monoclinic phase when x > 0.85. Various other phases (t’, t, t”, t”, and j) are recognized at intermediate compositions.\textsuperscript{[125]} Ceria-doped Zr-NS is well known for boosting oxygen storage capacity, enhancing the surface area and thermal stability, and reducing reduction-oxidation of O$_2$ storage promoters.

Rezaei et al.\textsuperscript{[126]} fabricated nanocrystalline CSZ via the Pechini process. Citric acid (CA) and ethylene glycol (EG) were used as complexation/polymerization reagents. The CA/EG ratio (TM denotes transition metal) was maintained at 1.8 mol, and the CA/EG ratio was varied (2, 5, 10). For CA/EG = 2, XRD results showed that a minute portion of the t-phase is converted into m-phase at 700°C. However, no such transformation occurred for other samples. A gradual rise in particle size and decrease in specific surface area were observed on raising the calcining temperature. The study also displayed that the CeO$_2$ content influenced the surface area (SA) and crystallite sizes. The crystallite size declined with an upsurge in the ceria content, and ZrO$_2$ crystallite growth was blocked by tempering it with ceria. A decrease in SA is also observed with a decrease in ceria content due to crystallite coarsening. Certain magnificently designed CSZ-based composite/hybrid nanostructures have been reported in Table 1 (entries 9–14).

#### 4.3.5. Ceria- and Yttria-Costabilized Zirconia (CYSZ)

CSZ has displayed many interesting and significant properties that were better than YSZ. Despite these advantages, CSZ suffers from the drawback of considerably lower erosion resistance than YSZ nanostructures. For resolving this issue, codoping of zirconia by ceria and yttria could be a promising candidate with excellent properties of binary stabilizing oxides, ceria and yttria. Reports have claimed that the CYSZ coating has shown superior properties to YSZ coatings because of high-temperature phase stability, increased thermal insulation, good corrosion, thermal shock resistance, and higher CTE. Various approaches, for example, sol–gel, hydrothermal, coprecipitation, and spray drying, have been employed for synthesizing t-CYSZ nanocrystals (10–100 nm).\textsuperscript{[127,128]}

Girolamo et al.\textsuperscript{[129]} fabricated CeO$_2$–Y$_2$O$_3$ costabilized zirconia TBCs using atmospheric plasma spray technique, and 1315°C was used as annealing temperature for various times. Ceria
delivered high-phase zirconia stabilization as no decomposition of phase was witnessed even after thermal aging. No formation of the m-phase was reported, and the c-phase was partially transformed into t-phase. An increase in crystal size was observed with an increase in annealing time, but a decrease in microstrains was observed. Columnar grains developed with the increment in the annealing time with respect to a preferential direction and, after long 50 h of heat treatment, were partially transformed into equiaxed grains. The acquired coefficient of thermal expansion of the CYSZ coating was significantly greater than data reported for YSZ. The microstructures exhibited sensitivity toward specific heat capacity (C_p), and the C_p values were reduced for high-temperature sintered coatings.

Hajizadeh-Oghaz et al.\textsuperscript{130} evaluated the impact of pH of the solution on the morphology of CYSZ NPs fabricated by a polymerizable complex route. In the Pechini process, the solution pH value plays a crucial part in balancing chemical reactions. The study illustrated that alteration in the acidity influenced the structure and the chemical reactivity of the polymeric network. Maintaining a constant acidic state is a must for the sols as the existence of ammonia huddles the construction of bridging bonds with citric acid. Such observation is illustrated in the morphological studies of powders. The main consequence of pH alteration is the destruction of esterification between EG and CA and affecting the Ce, Y, and Zr species and creating complexes among CA and mixed metals. The chelation degree of metal cations with carboxylic acids, which acts as an essential factor in the generation of CYSZ NPs, could be monitored by amending the precursor solution pH values. A decline in pH value reduces the chelation degree of metal cations. A list of some designed CYSZ nanostructures has been reported in Table 1 (15–19).

4.3.6. Scandia and Yttria Costabilized Zirconia (ScYSZ)

Due to severe operating circumstances, a reduction in the performance of the YSZ coatings has been reported.\textsuperscript{129} In the presence of molten salts, YSZ exhibited feeble hot corrosion resistance.\textsuperscript{131–133} Thenceforwad, multiple efforts have been made for improvising the hot corrosion and phase stability of YSZ TBCs. An utmost significant approach is to codope metal oxides. Studies have shown that a ScYSZ coating is better than a YSZ coating due to fracture toughness, higher strength, and stability against high temperatures.\textsuperscript{134–136} Based on the acid–base theory of ceramic corrosion, designed at the Naval Research Laboratory (NRL), scandia is recognized as a potential stabilizer and displays greater resistance toward molten sulfate–vandate attack.\textsuperscript{137} Further, Loghman-Estarki et al.\textsuperscript{138} evaluated the corrosion performance of SYSZ. The failure mechanism of the SYSZ TBCs was comprised of multiple steps, which are molten salt penetration through the coating defects; a chemical reaction between the molten salts and yttria to yield a minute amount of rod-type crystals of YVO; t-to-m conversion; generation of horizontal micro-cracks in the topcoat because of stresses induced due to generation of monoclinic zirconia and YVO_4 crystals; and generation of destructive compounds (NiCr_2O_4, NiO, and NiAl_2O_4). Further, Loghman-Estarki et al.\textsuperscript{138} estimated the sintering behavior and thermal stability of 5.5YSZ, 7YSZ, and 15YSZ nanostructures at 1480 °C. The findings described that the thermal stability of the SYSZ TBCs was longer than the 7YSZ TBCs because of the greater amount of t-phase. Moreover, the 7YSZ NS coating exhibited greater sintering resistance than nonstructured 5.5SYSZ TBCs. A few of the designed SYSZ nanostructures are listed in Table 1 (20 and 21).

4.3.7. Zirconia–Alumina Nanostructures/Nanocomposites (ZA NSs/NCs)

Zirconia and alumina, for the outstanding intrinsic characteristics, for instance, fracture toughness, hardness, chemical stability, Young’s modulus, and mechanical and wear resistance, are suitable for varied uses as fuel cells, sensors, implants, thermal barriers, etc. Many studies have shown that the amalgamation of alumina into zirconia’s matrix enhances the mechanical characteristics. Such materials include the characteristics of both zirconia and alumina. Such materials are called “alumina-toughened zirconia” (ATZ) materials. Such enhanced characteristics make zirconia and alumina promising candidates for multiple biological and other applications. Improved mechanical properties exhibited by the alumina–zirconia composites and nanocomposites are majorly due to the dispersal of the metastable tetragonal ZrO_2 particles into the matrix of alumina, which gets transformed into a stable m-phase under loading.\textsuperscript{139}

Lian et al.\textsuperscript{140} designed ZrO_2–30 vol% Al_2O_3 nanostructured composite coatings by following the atomic plasma spraying route. The fabricated coating exhibited a bimodal structure comprising nanoscaled equiaxed and columnar grains. Compared to ZrO_2 coating, the nanostructured ZrO_2–30 vol% Al_2O_3 composite coating amplified the microhardness from 5.7 to 8.4 GPa and roughness from 3.74 to 6.03 Am. Sintering parameters are found to play a critical role in the microstructure growth. Gadow et al.\textsuperscript{141} developed a tailored pressure-less sintering route for ATZ microcomponents to investigate the near-net-shape designing method’s full economic and technical potential. A decrease in the sintering temperature by more than 100 K was attained. Higher densities were obtained compared to the conventional sintering process. The pressure-less sintering process resulted in microstructure refinement and reduction in the GS of alumina by a factor of 2–3. Furthermore, Menezes et al.\textsuperscript{142} investigated the microwave hybrid fast sintering of ZA NCs. Via this process, NCs were successfully sintered to nearly whole density in short cycles of 35 min without using pressure. This method suppressed the ZA NC grain growth, attaining an average size and a particle size ratio of 2:1.

Moreover, Benavente et al.\textsuperscript{143} determined the microstructural evolution and mechanical features of microwave-sintered ZA NCs. Higher hardness, density, and Young’s modulus, homogeneous microstructure, and extraordinary fracture toughness characteristics were attained via microwave sintering compared to conventional sintering. Microstructure estimation has displayed nonsignificant growth of alumina grains representing a hampering impact by ZrO_2 particles on the Al_2O_3 growth. A list of a few zirconia–alumina nanostructures and nanocomposites is in Table 1 (22 and 23).
4.3.8. CSZ/Al Nanocomposite

Another type of zirconia-based nanocomposite is the CSZ/alumina (CSZ/A) nanocomposite. CSZ/A developed by Nawa et al. offers a strong and tough material for biomedical applications. CSZ/A material consists of interpenetrated intragranular nanostructures. These nanostructures have either nanometer-sized alumina or CSZ particles that exist with the submicron-sized CSZ or alumina grains, respectively. Numerous studies have confirmed a considerably greater mechanical strength of CSZ/A as compared to YSZ [157,158]. Such materials also exhibit maximum resistance toward low-temperature aging degradation into water-based situations such as an oral environment. In addition, CSZ/A permitted postsintering machining that needs robust milling equipment. This procedure attained highly accurate levels, and no additional treatment is needed. The CSZ/A system can resolve the clinical issues of YSZ because of the allowance for the optimal framework design and supporting forms.

Bera et al. evaluated the strength, slow crack growth (SCG), and fracture toughness of fabricated CSZ/A NCs as biomaterials for medical applications. The fracture toughness is estimated for long, sharp, and short cracks, and a great correlation is established among the crack types. The conversion of the t-t phase was the primary toughening mechanism. Enhancement in the strength and generation of the surface compressive induced stress resulted from the transformation over the surface of ground specimens. Komasa et al. assessed the impact of UV treatment on the CSZ/A NCs. Surface evaluation studies declared no structural or mechanical changes, but a decrease in the carbon content of the surface was observed. The material also displayed superhydrophilicity.

4.3.9. Gadolinia-Doped Zr-NSs

Apart from the aforementioned nanostructures, gadolinia-doped Zr-NSs have attracted significant attention of researchers across the world. Azad et al. fabricated layer-by-layer structured Gd$_2$O$_3$-doped ZrO$_2$ and CeO$_2$ on Al$_2$O$_3$ (0001) by employing plasma-assisted molecular beam epitaxy and estimated the nanoscale effects on the ion conductance. With increasing layer number, a rise in the oxygen ions conductivity was witnessed as compared to the bulk YSZ and Gd$_2$O$_3$-doped CeO$_2$ electrolyte. Furthermore, Bera et al. designed highly oriented extra-pure Gd$_2$O$_3$-doped thin films over a pure ZrO$_2$ (111)-buffered sapphire (Al$_2$O$_3$) substrate. The films produced over the thin layer of ZrO$_2$ (111) exhibited a highly oriented nature with a principal double domain orientation (111).

Wang et al. fabricated a 2 mol% Gd$_2$O$_3$-doped–4.5 mol% YSZ nanostructured coating via atmospheric plasma spraying method. The results indicated a classic microstructure comprising nanozones, splats, melted zones, microcracks, high-volume spheroidal pores, and nanopores. The GdYSZ coating displayed a lower resistance toward the destabilization of the metastable t-phase compared to YSZ. Doping of nano-YSZ with gadolinia reduced the thermal conductivity considerably as matched to conventional and nano-YSZ. Such a decline could be attributed to the Gd$_2$O$_3$ doping synergetic effect.

5. Optimized Approaches for Improving Surface Properties of Zr-NSs

The implantation of biomaterials into the human body commonly results in unavoidable interactions of implant surfaces with the surrounding biological environment. Therefore, designing and developing nanostructured materials with improved surface characteristics, i.e., surface morphology, composition, and microstructure, have gained considerable attention. Over the last decades, zirconia-based nanostructures have shown immense potential in numerous areas of science attributed to their exceptional mechanical performance, excellent cell adhesion, higher biocompatibility, and outstanding tissue response. These nanostructures further provide superior biological safety even at higher specific surfaces due to their chemical and bioinertness. However, the inert character of zirconia also causes some hindrance in their implantation to the target area. Other difficulties such as insufficient bonding to the surrounding bone and tissues, more extended healing periods for osseointegration, and the intrinsic brittleness of Zr-NSs, limit their clinical applications appreciably. Moreover, several infections lead to failure of the implantation as well.

Therefore, advancements in the overall surface designs are imperative to overcome these concerning issues. When performed at a microscopic level, the surface modifications enhance the roughness and wettability of the zirconia implant substrates and help promote and sustain the long-term osseointegration, one of the significant steps of dental implantation. Furthermore, these alterations significantly limit bacterial adhesion and infections, which is beneficial for a broad range of orthopedic implant applications. Consequently, various techniques pertaining to modifying surface characteristics of Zr-NSs have been developed extensively in recent years. These primarily include chemical etching, coating, UV treatment, oxygen plasma treatment, laser treatments, polishing, sandblasting, grinding, etc. In this section, we will briefly discuss these surface-improving techniques.

5.1. Chemical Etching to Improve Surface Properties of Zr-NSs

Nanostructured materials with better surface roughness (porosity) possess promising clinical applications and effectively induce notable changes in cellular and subcellular functions. A finely roughened surface does promote long-term osseointegration and exhibits superior bone response compared to smooth ones. Among the diverse techniques adopted to optimize the surface roughness and topographies of Zr-NSs, chemical etching treatments have been widely investigated. This process involves immersion of a nanostructured surface in strongly acidic solutions followed by rinsing and drying. Commonly available etching acids that have been used to etch zirconia successfully include hydrochloric acid (HCl), hydrofluoric acid (HF), phosphoric acid (H$_3$PO$_4$), etc. Amongst these, HF is considered one of the most promising etchants for zirconia. Chemical etching of zirconia with strong acids exerts substantial impacts on the surface characteristics. It can produce surfaces with nanoscale roughness, lower cytotoxicity level, and superior biocompatibility and when combined with microscale roughening treatments, it
could also generate synergistic effects.\textsuperscript{158} The effect of fluoride modifications has been evaluated, and the enhancement in osteoblastic differentiation and inhibition of bacterial growth after fluoride incorporation at zirconia implant surfaces has been reported.\textsuperscript{159} Later, Gahlert et al. and Saulacic et al. independently investigated the etching action of zirconia implants with hydrofluoric acid, and reported an increase in bone-to-implant contact (BIC) with higher implant exclusion torques.\textsuperscript{160,161} Recent research studies have been carried out by Vandro et al. to inspect the influence of HF etching on bond strength durability of Y-TZP polycrystals/resin cement. Experimental results revealed the highest bond strength values in both aging and drying conditions after the HF treatment of the glazed ceramic surface.\textsuperscript{162} Bergemann et al. investigated the influence of acid-etched YSZ surfaces on human primary osteoblast behavior (HOB) and reported a significant increase in cell maturation.\textsuperscript{163}

5.2. Coating to Improve Surface Properties of Zr-NSs

Various coating approaches have been used to advance bonding between the implant’s surface and the surrounding bone. Liu et al. demonstrated that coating of zirconia implants with polydopamine (PDA) could not only lead to the enhancement in proliferation and cell adhesion of human gingival fibroblasts (HGFs), but also reduce bacterial activity.\textsuperscript{164} Rochietta and co-workers investigated the moderation of the zirconia implants utilizing coating with hydroxyapatite (HA), a naturally occurring form of mineral calcium apatite.\textsuperscript{165} The coating was achieved by dipping the implants in a solution of NPs of HA. It was suggested that coated zirconia implants provided good stability and cell attachment. However, this treatment did not induce any pronounced effect on bond apposition and strength.\textsuperscript{166} Furthermore, Mick and co-workers demonstrated that coating the ceramic implants with a glass solder matrix provides an improved surface with sufficient roughness and adhesive strength that may promote osseointegration of ceramic implants.\textsuperscript{166} However, common issues associated with the coating treatments that need to be addressed are fracturing materials into multilayers, i.e., delamination, and inadequate adherence to the substrate.

5.3. Sandblasting to Improve Surface Properties of Zr-NSs

Sandblasting, also known as “abrasive blasting,” emerged as a viable and recommended surface treatment for inducing micro-scale roughness, irregularities, and increase in surface area and to promote better adhesion. Bioceramics are typically sandblasted with alumina particles as they have low cost and are hard and needle-shaped. Saleh et al. sandblasted zirconia samples with 110\(\mu\)m \(\mathrm{Al}_2\mathrm{O}_3\) particles. They described an increase in \(\mathrm{ZrO}_2\) surface roughness, which, in turn, provided much more efficient bonding with the veneering materials as compared to pristine zirconia samples.\textsuperscript{167} Later, Zhang et al. stated that sandblasting \(\mathrm{ZrO}_2\) before sintering increases the surface roughness significantly and improves the shear bond strength of veneering porcelain.\textsuperscript{168} The influence of certain factors, for instance, the impact angle, particle size, or pressure, on the surface topography has been investigated by some authors.\textsuperscript{169,170} Matinlinna and co-workers examined the effect of sandblasting angles and distance on surface roughness and resin cement bonding to \(\mathrm{ZrO}_2\) materials.\textsuperscript{171} Statistical analysis revealed that sandblasting at 75\(^\circ\) or 90\(^\circ\) angle resulted in high shear adhesive strength for resin cement to zirconia bonding. It has also been found that sandblasting could enhance osseointegration,\textsuperscript{171} flexural strength,\textsuperscript{172} wettability, and surface energy.\textsuperscript{173} However, this treatment suffers from several disadvantages as well. Sandblasting with different alumina particles could result in various alterations in surface morphology due to commonly encountered alumina contamination. It also causes t-to-m transformation by introducing surface flaws and defects, which could further reduce the strength and lifetime of zirconia ceramics loss of transformation capacity during cyclic loading.\textsuperscript{174,175}

5.4. Polishing to Improve Surface Properties of Zr-NSs

Polishing is a process that has been advocated to generate smooth, shiny, and reflective surfaces. To date, numerous studies have been reported examining the response of various biological cells to surface smoothness. In some cases, polished surfaces provide better advantages compared to roughened surfaces. Meyle’s group investigated the influence of surface topography and composition of implanted materials on the adhesion of soft tissues to the material surface.\textsuperscript{176} The results suggested that epithelial cells have better adhesion as well as proliferation on polished surfaces compared to sandblasted or acid-etched surfaces. In contrast, fibroblast cells possess a similar affinity for both surfaces. The zirconia surface is commonly polished using silicon carbide abrasive paper and diamond or silica suspension with a polishing machine.\textsuperscript{177,178} However, the macromolecular structure of zirconia causes several problems and limits the complete polishing of zirconia surfaces.\textsuperscript{179} Interestingly, Forster and co-workers evaluated in their research that out of three different polished materials, i.e., zirconia, cobalt–chromium, and lithium disilicate, zirconia exhibited a higher roughness of 25.3 nm. Subsequently, it was concluded that epithelial cells have minimum adherence on the polished zirconia surfaces as these cells favored smoother surfaces.\textsuperscript{179} Apart from its simplistic nature, the polishing process has its disadvantages as well. It causes several damages to the implant surfaces and may also result in various surface topographies and property alterations.\textsuperscript{180,181}

5.5. Plasma Treatment to Improve Surface Properties of Zr-NSs

Plasma treatment has emerged as an effective tool for increasing surface wettability, which could significantly improve the bonding between the resin and ceramic surface and promote proliferation and cell adhesion.\textsuperscript{182} It has been reported that the plasmatic processing of zirconia surfaces generates new reactive sites by changing functional groups on the surfaces.\textsuperscript{183,184} Moreover, this technique is time- and cost-efficient compared to the coating process and used effectively to convert the hydrophilic hydrocarbon surfaces of zirconia to hydrophilic surfaces. The impact of plasma treatment on the water contact angle of zirconia ceramics was tested by Bruno et al. The experimental outcomes strongly inferred that plasma treatment improved
the surface energy and wettability of zirconia surfaces with a contact angle reduced nearly half to that of the initial value.\textsuperscript{[185]} Sepanta and co-workers also performed similar experiments to examine the impact of plasma treatment on the bonding strength of zirconia. Zirconia discs of different thicknesses were subjected to plasma treatment with various working gases such as oxygen, argon, and an oxygen–argon combination. It was found that the bonding strength of zirconia enhanced significantly under the influence of all gases except oxygen, whereas a reduction in contact angle was observed with all gases.\textsuperscript{[186]} Furthermore, Valverde et al. illustrated that the micro-tensile bond strength of zirconia ceramic surfaces greatly increased after nonthermal plasma treatment.\textsuperscript{[183]} Yoshinari and co-workers reported appreciable enhancement in the surface wettability of zirconia disks after oxygen plasma treatment, resulting in superhydrophilicity.\textsuperscript{[155]} The influence of oxygen plasma treatment on the surface characteristics of zirconia ceramic and the biological responses of human osteoblast-like cells was evaluated by Shinhye Jyh et al.\textsuperscript{[187]} The experimental results suggested that plasma treatment increased the surface wettability and hydrophilicity of zirconia ceramics, thereby providing a good surface for biological cell growth. Furthermore, Shon et al. showed that helium plasma treatment on zirconia implants significantly increased osseointegration without altering the microtopography.\textsuperscript{[188]}

5.6. UV Light Treatments to Improve Surface Properties of Zr-NSs

Another successful approach to attain advanced properties of Zr-NSs is exposure or irradiation to UV light. This method of surface modification is easy to handle and helps in the reduction of active oxygen species over the material surface. Numerous investigations have discovered that implants exposed with UV light have demonstrated greatly boosted bone–implant contact because of superhydrophilicity.\textsuperscript{[189,190]} Han et al.\textsuperscript{[191]} have scrutinized the influence of UV light on ZrO₂ after UV-A (365 nm) or UV-C (243 nm) photofunctionalization for various time durations (15 min and 3 and 24 h). UV-A and UV-C-exposed samples neither exhibited deviations in the surface textural properties nor confirmed the existence of the monoclinic phase. It was also claimed that the UV-C irradiation significantly altered the aesthetic in color and enriched the MC3T3-E1 cell adhesion on ZrO₂ by photofunctionalization. Recently, Komasa et al.\textsuperscript{[149]} estimated the effect of UV treatment on CSZ/A nanostructured composite and revealed that the UV irradiation does not alter the mechanical or structural properties but reduces the carbon content of the surface material. Such a UV-irradiated material exhibited advanced superhydrophilicity. Also, the influence of UV photofunctionalization was determined on the cell attractiveness of ZrO₂ implants.\textsuperscript{[192,193]} The study revealed that a higher quantity of osteoblasts was attached on the surfaces. The results also stated that the UV-irradiated surfaces exhibited an alteration in the physicochemical properties and improved attractiveness toward primary human alveolar bone derived osteoblasts (PhABO). Furthermore, Tuna et al.\textsuperscript{[194]} estimated the influence of UV photofunctionalization on the surfaces of implant materials. The UV irradiation approach modified the physicochemical characteristics of the surfaces of the zirconia implants. Also, Brezavšček et al.\textsuperscript{[195]} evaluated the impact of UV irradiation on the osteoconductive capacity of Zr-NSs. The results clearly showed that the UV irradiation enhanced the osteoconductivity of zirconia-based nanostructures with distinct surface properties, which further leads to an amplification in the amount of bone formation and ultrafast-creation bone-implant integration.

5.7. Laser Treatments to Improve Surface Properties of Zr-NSs

Among different methods used for modifying the surface characteristics, laser treatment is another successful route for enhancing the surface properties of different materials. Laser treatment offers the benefits of versatility in amending the surface properties of biomaterials. It eliminates the risk of surface adulteration as there is no contact between the laser and material.\textsuperscript{[196]} Additionally, laser treatment has attracted significant attention because of its capability to enhance the wettability by changing the surface characteristics, which plays an important role in cell adhesion.\textsuperscript{[197]} Generally, the wettability test is conducted by positioning a liquid drop on a flat solid material surface. Further, the contact angle is applied for estimating the drop’s final shape. When the mean value of the water contact angle is lower than 90°, the material is hydrophilic, and when the values are less than 20°, the material is superhydrophilic. The lower the value of the water contact angle, the greater is the wettability, which makes the material more attractive for protein adsorption, osteoblast proliferation, and osseointegration. Hao et al.\textsuperscript{[197]} altered the MSZ’s surface wettability by applying a continuous-wave carbon dioxide laser. A sequence of numerous optical units was applied to provide laser treatment to MSZ via a laser head. In this study, the correlation between wettability, cell attachment, and laser parameters was estimated. The surface oxygen and surface energy were found to impact the wettability to a certain extent, but the influence of surface roughness was irrelevant. Cell adhesion and protein adsorption are adversely affected by wettability.

Laser treatment is also a promising candidate for modifying and enhancing the osseointegration of zirconia.\textsuperscript{[192–194,198–200]} Hao et al.\textsuperscript{[201]} defined an innovative route for the modification of YSZ surfaces to acquire a greater osseointegration index. The CO₂ laser treatment technique decreased the roughness but increased the wettability and surface energy of the surface. Moreover, laser treatment is used for promoting microgrooved surfaces over ZrO₂ implants. Peri-implant bone architecture, collagen fiber organization, and human cell metabolism could be altered by microtexture. Reports have revealed that the surfaces comprising regular geometry in a microrange could enhance the osteoblast proliferation, spreading, adhesion, and matrix protein synthesis.

5.8. Grinding and Machining to Improve Surface Properties of Zr-NSs

The grinding and machining process is an important part of the usual procedure of implant formation. Many reports have claimed that the grinding process could efficiently alter the mechanical properties of the zirconia-based implants.\textsuperscript{[1202]}
Muñoz-Tabarez et al.\textsuperscript{[203]} declared that the grinding of YSZ induces compressive residual stresses, which enhance the strength of the YSZ. Kosmać et al.\textsuperscript{[204]} reported a substantial decrease in strength when the dental grinding of YSZ was conducted at a higher rotation speed. However, Xu et al.\textsuperscript{[205]} stated that whether the strength of a Zr-NS will increase or not depends on the conditions of the grinding. The microstructural and crystallographic phase changes of YSZ dental ceramics were evaluated by Denry et al.\textsuperscript{[206]} The results have declared that the grinding process induces the generation of the strained tetragonal phase and rhombohedral zirconia phase, which leads to a significant rise in mean flexural strength and resistance toward crack propagation.

Studies based on machined zirconia implants have exhibited outstanding results for osseointegration and extra antibacterial activity. Scarano et al.\textsuperscript{[207]} scrutinized the BIC of machined zirconia implants for 28 weeks and stated 68.4% as the BIC percentage, without the existence of multinucleate or inflammatory cells. These results claimed that such machined implants could be osseointegrated and greatly biocompatible. Recently, in a review, Hafezeron et al.\textsuperscript{[208]} discussed the comparison between the BIC percentage of machined titanium and zirconia dental implants, following previously reported data.

5.9. Other Techniques to Improve Surface Properties of Zr-NSs

Apart from the techniques mentioned earlier, there are many advanced techniques, such as biofunctionalization and self-assembly, which have attracted significant attention for improvising the surface properties of Zr-NSs. Biofunctionalization, also called “bimimetic surface modification,” is a process that includes the immobilization of various biomolecules over the surface of materials to modify the biological responses and biochemical properties.\textsuperscript{[199]} This process allows the anchoring of organic components such as enzymes, peptides, and proteins over the surfaces of implants to monitor the implant–tissue interface\textsuperscript{[209]} and thus estimate the developed tissue type.\textsuperscript{[210]} The most widely used adhesive peptide is arginine-glycine-aspartate (RGD). Various adhesive proteins such as fibrinogen, fibronectin, and collagen possess RGD as cell recognition sites. Integrins conduct the identification of such RGD sequences. The integrins and adhesion proteins pair up to provide differentiation, cell anchorage, and growth signals. Moreover, the RGD peptide has been magnificently immobilized over the surface of YSZ and enhanced the biocompatibility of the biomaterials.\textsuperscript{[211]}

Another successful approach is self-assembly, which is an autonomous procedure in which constituents form structures and patterns minus the involvement of external intervention.\textsuperscript{[212]} Self-assembled monolayers (SAMs) are formed impulsively via the process of solution deposition by immersing a suitable substrate in a solution formed by dissolving an active surfactant into an opposite solvent (either organic or aqueous) or by vapor deposition or aerosol spraying of the active surfactants on the surface of the material. The driving force responsible for the self-assembly is precise interaction among the substrate surface and the surfactant’s head group. Most of the surfactants are comprised of three distinct parts: 1) the surface-active head groups that bind with the surfaces very strongly, 2) the terminal group located toward the monolayer surfaces, and 3) the alkane chain acting as a linker between the head and terminal group. The alkane group assists the packing of the monolayer molecules via Van der Walls interactions among the neighboring methylene groups, which orient and stabilizes the monolayers.\textsuperscript{[213–216]} Hung et al.\textsuperscript{[217]} successfully fabricated an ordered tetragonal mesoporous 16 mol% YSZ using evaporation-induced self-assembly (EISA) technique with Pluronic F127 (triblock copolymer) structure-directing agents. The studies confirmed the formation of an ordered mesopore arrangement described by a discrete face-centered tetragonal lattice.

6. Exploring Biological Responses toward Zr-NSs

Innumerable materials such as metals, polymers, ceramics, and their composites have been widely used to fabricate biological implants. For the last 100 years, metals and alloys have been used for fabricating biological implants for biomedical applications because of their certain advantages, such as ductility, mechanical properties, heat and electricity conductors, and biological/chemical compatibility. In 1895, the first ever metal implant (outside the dental implants) was designed, the internal fixation “lane plate” generally used for bone fractures.\textsuperscript{[218]} The progress of recent implants was originated with the starting of cobalt–chromium and stainless-steel alloys in the early 1900s. After that, in the mid-20th century, metal implants comprising cardiac, dental, and orthopedic devices were announced.\textsuperscript{[219,220]} In the 1950s and 1960s, the first ever total hip replacement comprising metal-on-metal designs with cobalt–chromium alloys was introduced.\textsuperscript{[221]} With the modernization of technology, metal implants have secured their position in almost all biomedical fields to treat or control a wide range of diseases. Due to continuous development, various varieties of metal implants are known and have exhibited outstanding efficiency in the biomedical field.

Development of synthesizing procedures, ceramic materials such as zirconia-based ceramics, glass ceramics, and polycrystalline alumina ceramics have gained importance as dental materials. Particularly, zirconia is used for coping and crowns for natural teeth and for fixed partial dentures. Due to the excellent resistance toward fracture and strength, zirconia has been exploited greatly in dentistry. Moreover, the market expense of ZrO$_2$ is much more constant than the noble metals’ expenses. Furthermore, as zirconia delivers sufficient esthetic properties plus lesser risk for discharging metal ions, zirconia implants are an excellent candidate for replacing conventional titanium implants for metal-allergic patients. Various reports have demonstrated meaningfully reduced bone damage with zirconia implants than titanium implants. Also, zirconia implants have a tendency of accumulating lesser bacterial plaque compared to the conventional titanium implants, therefore exhibiting the higher biocompatibility of the materials.\textsuperscript{[222]}

When a biomaterial is implanted into the body, it might potentially generate host inflammatory responses. Acute inflammatory responses, originated by the injury toward the tissues, is the reason why defining biological responses toward implants in shorter and longer durations of time is necessary. The sternness of the acute inflammatory responses is also influenced by the location...
and type of surgical practice, and the biological host’s makeup. Some of the other factors that influence the biological responses toward an implant are the type of implant, its physicochemical properties, composition, relationship with the host, degradability, and generation of byproducts. The modern implants are designed to stimulate a suitable cellular response to create implant integration and hinderance from perpetuation, resulting in foreign-body reactions and chronic inflammation and reducing the implant functions.

During the implantation of any device, the three significant concepts related to the bone responses are osteoconduction, osteoinduction, and osseointegration. Osteoconduction represents the growth of the bone on a surface. The surface that permits the bone growth either on the surface or down into channels, pipes, or pores is the osteoconductive surface. In osteoinduction, the undifferentiated, primitive, and pluripotent cells are stimulated to translate into a bone-forming cell lineage. Another definition proposed for osteoinduction is that it is a process that induces osteogenesis. This phenomenon is mostly observed in the healing of all types of bones. It also indicates the immature cells’ recruitment and stimulation to convert into preosteoblasts. During the bone-healing condition (such as a fracture), most of the role is dependent on the osteoinduction. The term “osseointegration” was initially devised as a direct contact amongst the implant and the living bone. It is also defined as a route in which clinically asymptomatic rigid fixation is attained and maintenance of the alloplastic materials in bone during the functional loading. These three phenomena are not similar but are interconnected. The phenomenon of osteoinduction contributes to the typical bone-healing process and is a reason for newly developed bone. The implanted implant might also act as osteoinductive, but it is not a precondition for the bone induction process. Further, both the osseointegration and osteoconduction phenomena are dependent on biological factors and responses toward the foreign material. Zirconia implants have exhibited osteoconductive behavior.

Osteoconduction means that bone grows on a surface. ZrO₂ implants, due to admirable topographical configuration, biocompatibility, wettability, and physicochemical features, have exhibited good osteoconductive behavior. Moreover, it has also been investigated that modifying surface characteristics of zirconia implants results in enhanced osteoconductivity. Att and co-workers showed that the osteoconductive capacity of zirconia implants was notably improved by the UV treatment method, resulting in an accelerated cell attachment, cell spread, and the fast establishment of bone-implant integration. Wu et al. demonstrated that oxygen plasma treatment significantly increased the wettability of zirconia implants, which helps to retain stable surface hydrophilicity and in turn promotes better osteoconductive behavior and cell proliferation.

Bone tissue response is affected by various factors, such as implant design, implant material, porosity, surface conditions, bone status, implant loading conditions, and surgical techniques. Many surface properties affect the quality and speed of the osseointegration, for instance, the topography, surface energy, surface chemistry, wettability, charge, crystallinity, and crystal structure, chemical potential, roughness, and coexistence of impurities. Important factors such as free surface energy and wettability are directly linked with the roughness. Further, osteoblast adhesion is associated with the hydrophilicity/hydrophobicity of the surface and the degree of roughness. Compared to hydrophobic surfaces, hydrophilic surfaces are superior for blood coagulation, and studies have shown that hydrophilic treatment over zirconia increases osteoblast-like cells’ initial attachment. Also, reports have claimed that enhanced hydrophilicity would speed up the osseointegration in dental implants.

Roughness, a scale-based factor, is classified as micro- and nanoroughness. Both these scales affect the tissue response at distinct levels. Microroughness strongly influences the bone response. On surfaces with microroughness, osteoblast discharge features enhance the osteoblast differentiation and reduce the creation and action of the osteoclast. Experimental findings revealed that osseointegration could be accelerated and improved by numerous roughening processes. The study also reports the existence of an optimal range within the micrometer scale. However, nanoroughness could influence the stem-cell and osteoblast behavior. The surfaces with nanoscale features have positively influenced the spreading, adhesion, motility, adhesion selectivity, and differentiation, which state that the nanoscale modifications could trigger some cellular phenomena. Moreover, a mixture of micro- and nanoroughness could demonstrate synergistic properties. It has also been displayed that the fractal parameters influence cell behavior. Further, Dalby et al. have demonstrated that the nanoscale disorder effectively stimulated the human mesenchymal stem cell (hMSC) formation in scarcity of osteogenic supplements.

The biomedical implants offer a surface for bacteria’s adhesion, and these bacteria could proliferate and create biofilms and affectedly enhance the fight toward therapeutic agents. This phenomenon is sometimes called “race for the surface,” as it is a race between host cells and bacteria. The need to eliminate pathogens has become a strong topic of interest in designing surfaces that could prevent infections. Several surface-engineering approaches have been introduced to attain such surfaces that could deal with uninvited infections.

7. High-Performance Biomedical Applications of Multimodel Zr-NSs

Excellent mechanical properties, higher biocompatibility, and aesthetics are the properties of zirconia that brought zirconia nanomaterials in demand for numerous biomedical applications, which include dental implants, bone implantation, drug delivery, biosensing, water and air purification, fuels, and solar cells. This section summarizes the major fields of biomedical application areas Zr-NSs has played a significant role in.

7.1. High Performance of Multimodel Zr-NSs in Dentistry

Due to the increased appeals of patients worldwide for replacing metal-free solutions with materials that are more biocompatible, have an aesthetic appearance, and attain good mechanical characteristics, ceramic materials have been frequently used in dentistry for a very long time. In the need to have more excellent
ceramic applications compared to conventional materials, zirconia-based NCs have appeared as a sensational branch of ceramic materials in the field of dentistry. Therefore, a lot of investigations have been put forward over the past several decades aimed at improving the properties of Zr-based NCs, and thereafter exploring their potential applicability to dentistry. Also, the dental wear and chipping should be minimized, along with health and optical requirements, which are based on various critical parameters, such as 1) tensile and flexural strength, 2) nontoxicity, 3) excellent chemical stability, 4) biocompatibility, 5) transluency, 6) great crack resistance, 7) well-defined thermal expansion coefficient, 8) decrease in veneer layer thickness, and 9) high color variability.

Recently, the robocasting additive manufacturing (AM) method was used to design nanostructured zirconia, and the suitability of the obtained nanostructured zirconia material was tested for dental applications. This study revealed that the AM samples are more biocompatible, less dense, and more porous than samples generated by the conventional subtractive manufacturing (SM) method (Figure 10). Chewing simulation tests carried out on dental cusps of humans with artificial saliva showed that the dental wear was lower with AM counter body than with SM samples. Overall, AM-processed samples are very efficient for dental restorations.

Johannes and co-workers found a different route for dental restoration. They developed a novel lithium disilicate glass ceramic, spray coated it on a separately designed ZrO2 matrix, and finally passed it through tempering treatment. Alkali metal ions are required to form niobate and silicate crystals, which further leads to the formation of the niobate–silicate glassy phase. This combination fulfilled the aesthetic demands and showed the high functionality required for dental restoration. The method introduced by this group is an intermediate one between spray coating and veneering.

YSZ ceramics have shown excellent properties in dental applications. Recently, the effects of various processing parameters such as core surface roughening and the feldspathic veneer fusing atmosphere were investigated over a dental zirconia core. The wetting behavior shown by the zirconia core due to molten veneer was estimated by employing the sessile drop method for 0–120 min at 990 °C. The results displayed that no wetting behavior was observed when the contact angle was greater than 90° at conventional conditions. On varying the firing atmosphere or surface roughening, high effects were noted on wettability.

Y-TZP is the strongest and most long-lasting dental restoration ceramic over decades due to its high survival rate. The advanced Y-TZP ceramic material 3Y-TZP is a frequently used ceramic, especially for its posterior-fixed restoration biocompatibility and brilliant mechanical characteristics (strength, wear resistance, and fracture toughness). However, the generation of agglomerates in 3Y-TZP powder deteriorates the mechanical properties of 3Y-TZP. A recent study evaluated the microstructural and mechanical properties of 3Y-TZP designed by an optimized combination of colloidal processing and CIP. Polyethyleneimine (PEI) was used as a dispersant for the colloidal processing step, followed by the adjustment of pH to attain colloidal stability. Then 3Y-TZP was subjected to CIP, and the density, flexural strength, phase structure, hardness, and microstructure were compared with those of 3Y-TZP, which was not subjected to CIP. 3Y-TZP structures generated without CIP resulted in 93% density,
the one produced by CIP treatment exhibited 100% tetragonal phase content with greater mechanical properties, homogeneous microstructures, and higher density. Also, characteristics of 3Y-TZP blocks that were applied for CAD/CAM dental restorations were studied by Santos and co-workers.[253]

Recently, Y-TZP ceramic has also been doped with metals such as iron and aluminum, and sintering effects were also investigated on the thermal behavior, structure, biocompatibility, and morphology of Y-TZP.[252] Ceramics with stoichiometries, $Zr_{0.85}Y_{0.12}M_{0.03}O_2$ and $Zr_{0.88}Y_{0.12}O_2$ (M = Fe, Al), have been designed via the Pechini method, which were further sintered for 10 h at 1300 °C. Sintered discs were implanted in a rat’s oral mucosa for 6 months. Local tissueal studies were evaluated using optical microscopy. Doping with iron and aluminum improved the Y-TZP’s powder sintering behavior. Doping with metals also strongly affected the morphology of sintered. Biocompatibility tests revealed the formation of fibrous connective tissues around tested samples. No adverse reactions were observed in discs implanted in the oral mucosa of rats, making these doped ceramics promising candidates for dental prosthetics.

Dental restorations milling (dentures, bridges, or crowns) from ZrO$_2$ blocks and blanks has been facilitated by recent progress in CAD and CAM milling systems. Zirconia blanks can be either presintered or fully sintered.[253] Soft machining of blocks is a faster and easier method compared to hard machining. Soft-machining blocks are presintered (850–1200 °C) to achieve minimal (40%) theoretical density. In a recent study, researchers described a novel method for preparing dental blocks by zirconia–alumina nanocomposites. The obtained powder was fabricated via the Pechini method, which were further sintered for 10 h at 1300 °C. Sintered discs were implanted in a rat’s oral mucosa for 6 months. Local tissueal studies were evaluated using optical microscopy. Doping with iron and aluminum improved the Y-TZP’s powder sintering behavior. Doping with metals also strongly affected the morphology of sintered. Biocompatibility tests revealed the formation of fibrous connective tissues around tested samples. No adverse reactions were observed in discs implanted in the oral mucosa of rats, making these doped ceramics promising candidates for dental prosthetics.

Conventional approaches used for adhesive bonding are not effective for zirconia restorations. Freshly, Zeta Etching Solution (ZES) was announced to etch the zirconia surface. But the influence of ZES on the mechanical properties and bond strength was not clear. Therefore, Ansari and co-workers conducted in vitro study to evaluate the impact of ZES on the mechanical properties and bond strength of zirconia.[255] The in vitro studies concluded that ZES considerably boosted the bond strength but was not effective in enhancing the surface hardness. A different approach was introduced to synthesize polyvinylpyrrolidone/Zr(OPr)$_n$ fibers by the electrospinning method.[256] Upon calcination at 850 °C ZrO$_2$ nanofibers with a diameter of about 98 nm were successfully fabricated in the tetragonal phase.

Zirconia ceramics could also be created by various hot isostatic pressing (HIP) conditions.[257] The effect of HIP on the compressive strength, density, phase transformation, and Young’s modulus were also evaluated. For this study, the sol–gel method was used to fabricate CaO-stabilized zirconia material using calcium isopropoxide, zirconium propoxide, and 2-methoxyethanol. The obtained powder was processed through HIP treatment to obtain a dense ceramic finally. With 70 nm average particle dimension, pure cubic phases were obtained when the zirconia powder was calcined at 500 °C. Presintered samples showed a single-crystalline cubic form, whereas HIP-treated samples showed monoclinic cubic or monoclinic tetragonal phases. Dense ceramics with 94% relative density were obtained after HIP treatment. A ZrO$_2$–CaO ceramic also displayed high compressive strength (500–708.9 MPa) and elastic behavior (Young’s modulus 1739–4372 MPa). ZrO$_2$–CaO also showed biocompatible behavior tested on MG63 cells.

Coating the zirconia ceramic dental restorations with nanostructured alumina coating (NAC) resulted in durable and strong bonds compared to the air-particle abrasion used clinically. However, the generation of the NAC must be easy and could be synthesized in dental laboratories regularly. Recently, the effects of various firing procedures used in dental laboratories, such as veneer, glaze, and regeneration, were evaluated.[258] Also, the combination of NAC calcination with high-temperature firing methods results in an acceptable Y-TZP–resin bond superior to the bond strength shown by 10-methacryloyloxydetyl dihydrogen phosphate (MDP) containing primer and low-pressure abrasion.

A novel and innovative route was implemented in order to improve the microstructural and compositional features of zirconia-based composites. 84 vol% fully dense Ce-TZP with equi-axed 8 vol% Al$_2$O$_3$ and 8 vol% elongated SrAl$_2$O$_3$. Recently, Reveron et al. estimated the influence of the stabilization degree of zirconia on mechanical and transformability characteristics of a Ce-TZP–Al$_2$O$_3$–SrAl$_2$O$_3$ hybrid composite. Biaxial flexural strength, single-edge V-notched beam, and Vickers hardness investigations illustrated the high impact of the ceria concentration on the mechanical properties. Zirconia composites with 11 mol% and higher CeO$_2$ displayed no plasticity, brittle classic behavior, and low strain failure, whereas CeO$_2$ content of 10.5 mol% or lower showed larger induced plasticity and negligible strength data dispersion. Composites with 10.5 mol% CeO$_2$ exhibited the highest fracture toughness and biaxial bending strength values. These composites exhibited high strength, ductility, and toughness, which could be very helpful in perfect reliability and longer durability of dental implants. A different route for zirconia ceramics was developed by the Li group by infiltrating a polymer in zirconia ceramics. A study was conducted to estimate its mechanical and microstructural behavior with respect to the presintered temperature. The results showed that different polymer contents and porosities were obtained at different presintered temperatures. The zirconia composite, when presintered at 1150 °C, showed tooth-like properties, making it a promising, easily produced material in dental clinics. A detailed comparative analysis was carried out by Gahlert et al. in order to examine the osseointegration of microstructured zirconia implants in comparison with sandblasted and acid-etched (SLA) titanium implants. It was revealed that acid-etching of zirconia implants substantially enhances bone apposition resulting in the removal torque (RTQ) values which were equivalent to that of Ti-SLA.[169] (Figure 11).

7.2. High-Performance of Multimodal Zr-NSs in Bone Implantation

Zirconia NPs have gained the attention of researchers and scientists around the world as efficient biomedical materials. Initially, zirconia biomaterials were primarily used only for hip replacements,[261] but later, zirconia composites found applications in bone cement,[262] dental prostheses and implants,[263] and bone graft substitutes.[264] Radiographic and microscopic studies tested in animals revealed the biocompatibility of zirconia implants. These studies also illustrated that bone apposition occurs directly on implanted surfaces without cellular infiltration and generation of any gaps.[231]
Regardless of numerous studies focused on zirconia ceramics, less attention was paid to explore the impact of surface-modified zirconia ceramic implants on bone tissue response. Therefore, many studies were conducted by modifying zirconia bioencamers' surface and evaluating their biological and mechanical properties.

Scarano et al. studied the bone response toward the zirconia ceramics implanted in New Zealand’s white male rabbits. Four implants were embedded into the rabbit’s tibia. The rabbits were euthanized after 28 days, and 20 implants were recovered. Newly formed bones were detected near the zirconia surface under a Leitz Laborlux microscope in normal transmitted light. The zirconia bone–implant interface appeared to have no gaps, multinucleated cells, fibrous tissue, and inflammatory cell infiltrate. In short, these zirconia implants are osteoconductive and highly biocompatible.

Titanium (Ti) and titanium alloys, because of the high specific strength and excellent corrosion resistance, are extensively applied as orthopedic and dental implants. But after a bone fracture, when a Ti alloy is used for bone fixators, the Ti alloy can develop new bone, which might cause refracture after removing fixators once the bone is healed. Recently, Takada et al. described a study built on the inhibitory effects of zirconium coating on titanium bone bonding in the rat femur. Ti implants and Zr-coated Ti implants were implanted in the left and right femur for evaluating these effects. After 4 weeks, the femurs and implants were removed, and a pull-out test was used to estimate the shear strength of both the implants with bone. The results displayed that the Zr coating over Ti implants inhibited the bone bonding among bone and Ti implant in vivo. Therefore, a Zr coating over Ti and Ti alloy implants could be useful in preventing refracture during the removal of Ti implants after bone healing.

Gain et al. used a pressure-less sintering process for fabricating porous monolithic hydroxyapatite (HA) and hydroxyapatite–zirconia (Hap–ZrO₂) NCs using a pore-forming agent, i.e., polymethyl methacrylate (PMMA). The elastic modulus, compressive strength, and pore morphology changed affectedly with the rise of pore-generating agents. Interconnected microstructures were obtained for HA and Hap–ZrO₂ composites. Hap–ZrO₂ NCs presented better elastic modulus and compressive strength than HA.

The generation of wear particles of PMMA bone cement in joint replacement devices has always been a contest. Many efforts have been made to reduce the wear of the articulating joints. Therefore, Schunck et al. assessed the surface tophography of PMMA bone ceramic with a zirconia radio pacifier to assess the surface roughness and morphology. The results displayed that mulberry-shaped zirconia crystal agglomerates were initially ground and truncated on flat surfaces and to end torn out of the matrix. Also, the assessment of in vitro PMMA-on-PMMA articulation declared the exposure of zirconia agglomerations to fatigue, pullout, and fatigue. Results have also shown the dissemination of zirconia NPs to different storage organs and lymph nodes. Pattnaik et al. also proposed a diverse route for bone-tissue engineering. In this study, the freeze-drying technique was used to combine nanosized silicon dioxide (Si), chitosan (CS), and ZrO₂ and design a biocomposite scaffold. Such a porous biocomposite framework was appropriate for cell colonization and infiltration. Recently, Pobloeh et al. used the mimic concept of natural bone surface for fabricating four differently coated zirconia-toughened alumina (ZTA) ceramic implants with varied thickness and evaluated their osseointegration. The study also investigated cancellous bone integration. Applicability of zirconia nanostructures in the field of bone implantation are mentioned in Table 2.

7.3. High-Performance Biosensing Application of Multimodel Zr-NSs

Biosensors are integrated miniaturized devices comprising biological elements acting as sensing elements (such as enzymes, antibodies, nucleic acids, receptor proteins, tissue sections, or whole cells) coupled with physical transducers (electrochemical, optical, or mass) for signal detection. Biosensors display applications in medical diagnosis and other biomedical fields because of their specificity, portability, cheaper rate, and fast response time. Based on the transducers used, biosensors could be classified as electrochemical biosensors, amperometric biosensors, potentiometric biosensors, conductometric biosensors, optical biosensors, thermometric biosensors, and piezoelectric biosensors. Numerous strategies have been used for fabricating biosensors, and a few of the promising ones are given subsequently.

7.3.1. Multimodel Zr-NS-Based Immunosensors

In 2014, Kumar et al. proposed a novel, saliva-based, efficient, simple, and label-free zirconia-based biosensor to detect oral cancer. The ZrO₂NPs were synthesized using the hydrothermal route, and 3-aminopropyl triethoxy silane (APTES) was further used for silanization. The electrophoretic deposition technique resulted in APTES/ZrO₂/ITO films. Furthermore, these films were immobilized by antibodies (CYFRA-21-1). These saline...
antigens act as biomarkers for oral cancer detection. This engineered biosensor displayed a wide detection range (2–16 ng/mL), high sensitivity, and 0.08 ng/mL as the detection limit. Therefore, the saliva-based biomarker opened many doors for the fabrication of zirconia-based biosensors for cancers.

Also, Kumar et al.\[276\] fabricated an immunosensor by decorating nanostructured zirconia over rGO and tested it for the detection of the CYFRA-21-1 biomarker in the saliva of suspected oral cancer patients. The APTES/ZrO\(_2\)–RGO/ITO was formed by the silanization and electrophoretic deposition method. This APTES/ZrO\(_2\)–RGO/ITO was functionalized with antibodies (anti-CYFRA-21-1) and BSA molecules. The generated immuno-electrode (BSA/anti-CYFRA-21-1/APTES/ZrO\(_2\)–RGO/ITO) exhibited higher selectivity and sensitivity, and a broad linear detection range.

To fabricate a biocompatible, nontoxic, and efficient biosensor, it has become crucial to modify the desired nanomaterial surface with functional groups such as –OH, –NH\(_2\), and –COOH.

### Table 2. Applicability of ZrO\(_2\) nanostructures in the field of bone implantation.

| Authors               | In vivo/in vitro/animal | Studied material                  | Result assessment method          | Results                                                                 | Conclusions                                                                 |
|-----------------------|-------------------------|-----------------------------------|----------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Abousheib et al.[361] | New Zealand white male  | Infiltration-etched zirconia      | SEM, histometric analysis        | SEM images displayed the intergrain surface porosity of implants        | SIE displayed a higher degree of osseointegration than as-sintered zirconia and titanium implants |
|                       | rabbits                 | implants                          |                                  | Histometric analysis – 1) after 4 weeks, mean BIC for SIE zirconia implant = 65.38 ± 5.7, for as-sintered zirconia implant = 53.30 ± 4.2, and for titanium implants = 56.93 ± 3.9; 2) after 6 weeks, mean BIC for SIE zirconia implant = 75.01 ± 5.1, for as-sintered zirconia implant = 62.14 ± 2.8, and for titanium implants = 68.31 ± 4.2 |
| Al Farraj et al.[339] | Rabbits                 | Zr and Ti implants                | Histometric analysis and BIC percentage | BIC values of implants                                                  | Zr and Ti implants exhibited analogous BIC values; HA coating did not improve the bone integration |
|                       | (Figure 12)             | Hydroxapatite-coated Zr and Ti    |                                  | (Zr-uncoated) = 45.1 ± 14.8, (Ti-uncoated) = 45.5 ± 13.1, (HA-coated Zr) = 60.3 ± 17.1, (HA-coated Ti) = 59.8 ± 16.4 |
| Oliva et al.[362]     | Sheep                   | Y-TZP                             | Histology and histomorphometric analysis, removal torque test (RTQ) | Histological evaluation displayed direct BIC and no foreign body reaction or inflammation; BIC = 79.5–79.9%, RTQ values = 75–83 N cm. |
|                       |                         |                                   |                                  | CeraRoot zirconia (Y-TZP) implants showed biocompatibility and osseointegration |
| Depprich et al.[363]  | Göttinger minipigs      | Y-TZP                             | SEM analysis achieved at bone–implant interface | Bone attachment was observed within 1 week; osseointegration without interposition was detected after 12 weeks |

### Figure 12. A) The type of implants used in Al Farraj et al.[339] (left titanium, right zirconium). B) Images showing the articular approach used for the implant installation and final positioning. C,D) The light micrographs displaying the Zr-HA implant. The Zr-HA implant is located in the trabecular bone, which appears to be directed into the implant threads. No crestal resorption is witnessed. Reproduced with permission. Copyright 2018, Springer Nature.
Additional linkers are required to simplify the nanomaterial modifications. Numerous linkers such as 3-mercaptopropyl triethoxy silane (MPTES) and APTES have been used for covalent bridging between biomolecules and nanomaterials. However, such linkers destroy the mucous membranes of the liver, kidney, respiratory tract, and nervous system. Therefore, the introduction of nontoxic linkers could be advantageous for the functionalization of nanomaterials. One of the nontoxic organic compounds having the capability of acting as great linkers is amino acids, primarily due to the availability of both amine and carboxylic acid groups.

Further, Kumar et al. proposed a novel biosensing platform by using amino acids as linkers to functionalize nZrO$_2$ NPs to fabricate label-free, noninvasive, and effective biosensors for oral cancer detection. The hydrothermal process was used to synthesize nanostructured zirconia, with 4.5 nm as an average crystallite size. ZrO$_2$ NPs were further functionalized by serine by a simple chemical process. MTT assay on the HEK 293 human cell lines was used to study the cytotoxicity of serine/nZrO$_2$. The cytotoxicity studies revealed the biocompatible nature of serine/nZrO$_2$. Then, serine/nZrO$_2$ was electrophoretically deposited on an ITO-coated glass electrode. Furthermore, serine/nZrO$_2$/ITO was functionalized with monoclonal antibodies (anti-CYFRA-21-1), and BSA was used as a blocker for nonspecific binding sites of the developed immunoelectrode. The designed BSA/anti-CYFRA-21-1/serine/nZrO$_2$/ITO immunoelectrode showed greater detection efficiency as an oral cancer biomarker. This biomarker demonstrated a wide linear detection range from 0.01 to 29 ng mL$^{-1}$ along with an amazing detection limit and fast response time toward the CYFRA-21-1 antigen.

Further, Gupta et al. fabricated a zirconium dioxide–rGO (ZrO$_2$–rGO) nanocomposite, functionalized the ZrO$_2$–rGO nanocomposite with L-methionine, and used it for an immunosensor application (Figure 13). Morphological studies revealed that ZrO$_2$ NPs got decorated over rGO sheets. The meth–ZrO$_2$–rGO nanocomposite displayed improved wettability and biocompatibility. Furthermore, a BSA/anti-OTA/meth/ZrO$_2$–rGO/ITO immunoelectrode (where OTA stands for ochratoxin A) fabricated by electrophoretic deposition and immobilization of antiochratoxin A antibodies demonstrated a wide linear detection range with high sensitivity and incredible detection limit. The rGO reduced the aggregation of ZrO$_2$ NPs and enhanced the electrochemical properties of the ZrO$_2$–rGO nanocomposite.

Gupta et al. further synthesized pure tetragonal ZrO$_2$ NPs by Al$^{3+}$ ion doping in the ZrO$_2$ lattice. The presence of coordinating oxygen vacancies on the surface of ZrO$_2$ improved the surface charge and adsorption capability (Figure 14A). These enhanced properties further increase the affinity of Al$^{3+}$-doped ZrO$_2$ NPs for biomolecules’ immobilization. The fabricated immunoelectrode, BSA/anti-OTA/Al$^{3+}$-ZrO$_2$/ITO, exhibited improved parameters and 93.3–99.2% of OTA’s recovery from the spiked samples.

![Figure 13. A) Stepwise synthesis of the BSA/anti-OTA/meth/ZrO$_2$–rGO/ITO immunoelectrode. B) SEM images of (a) meth/ZrO$_2$–rGO/ITO electrode and (b) anti-OTA/meth/ZrO$_2$–rGO/ITO immunoelectrode. Reproduced with permission.[278] Copyright 2017, Royal Society of Chemistry.](image-url)
Further, Gupta et al.\(^{[280]}\) proposed a novel approach for designing amino-functionalized zirconia-based nanocomposites (Figure 14B). The presence of NH\(_2\)C in the designed nZrO\(_2\)–NH\(_2\)C nanocomposite inhibited the formation of the aggregation of ZrO\(_2\) and enhanced the electrochemical behavior of the nZrO\(_2\)–NH\(_2\)C nanocomposite. Furthermore, the nZrO\(_2\)–NH\(_2\)C nanocomposite exhibited improved mechanical strength and hydrophilicity compared to a bare nZrO\(_2\) nanocomposite. The engineered BSA/anti-OTA/ nZrO\(_2\)–NH\(_2\)C/ITO immunosensor displayed selective detection of OTA.

Bagbi et al.\(^{[281]}\) fabricated a novel nanocomposite comprising ZrO\(_2\) NPs and biopolymer gelatin-A (GA) electrodeposited on an ITO-coated glass substrate (Figure 14C). Further, a GA-ZrO\(_2\)/ ITO electrode was immobilized by monoclonal antibodies, specifically for *Vibrio cholera* (Vc) detection. The GA–ZrO\(_2\) nanocomposite offers a porous structure with a higher surface area for increased loading of antibodies to give enhanced biosensing properties.

### 7.3.2. Multimodel Zr-NS-Based Genosensors

Recently, Das et al.\(^{[282]}\) immobilized 21-mer oligonucleotide probe (ssDNA) over ZrO\(_2\)/Au surface without using any linker and used the nanocomposite as a specific biomarker for *Mycobacterium tuberculosis*. The affinity between oxygen atoms of DNA phosphoric group and zirconium played an essential part in designing such a biosensor. The DNA–ZrO\(_2\)/Au displayed 60 s as the response time and linearity as 640–0.065 ng L\(^{-1}\). This biomarker was also stable for 4 months when stored at 4 °C. Solanki et al.\(^{[283]}\) fabricated a DNA-based biosensor by immobilizing the O1 gene 24-mer ssDNA on NanoZrO\(_2\)/ITO to detect *V. cholerae*. The ssDNA/NanoZrO\(_2\)/ITO bioelectrode showed higher sensitivity toward genomic DNA compared to complementary DNA. Both the genomic and complementary DNA displayed hybridization time as 5 min and response time as 1 min. This DNA-based sensor executed higher specificity for *V. cholerae*. ssDNA/nano-ZrO\(_2\)/ITO showed more excellent stability for 15 weeks when stored at 4 °C.

Fahrenkopf et al.\(^{[284]}\) engineered a novel route for the immobilization of nucleic acids for high-electron transistor-based biosensors. The five-terminal phosphate group of nucleic acids coordinated with the metal oxide surface and semiconductor. In this study, DNA was directly immobilized on GaN, ZrO\(_2\), AlGaN, and HfO\(_2\) without any linkers. This immobilization technique can generate electrical-based detectors, such as high-electron-mobility transistors (HEMTs) and field-effect transistors (FETs). Solanki et al.\(^{[285]}\) designed a DNA biosensor by the immobilization of 17-base-terminal ssDNA on a nano-ZrO\(_2\) film derived by the sol–gel method (Figure 15A). The electrochemical results stated that the nano-ZrO\(_2\) provided the enhanced...
electron-active surface area for increased electron transport after the immobilization of ssDNA. The obtained bioelectrode (ssDNA/NanoZrO2/ITO) exhibited highly sensitive hybridization detection of complementary DNA.

In 2013, Yang et al.\cite{286} compared the ZrO2 electrochemically reduced graphene oxide (ERGNO) nanocomposites, obtained by a single step (ZrO2–ERGNO) and stepwise electrodeposition (ZrO2/ERGNO), for DNA sensing by using methylene blue as an indicator (Figure 15B). The structural studies displayed the fine globular nanostructures for ZrO2–ERGNO, but an agglomeration of massive microstructure occurred in ZrO2/ERGNO because of the absence of oxygen functional groups due to the better affinity of oxygen-containing groups toward ZrO2 deposition. DNA probes were immobilized on the ZrO2-based nanocomposites due to the strong binding between the phosphate group of DNA and zirconia films. DNA-immobilized nanostructured ZrO2–ERGNO was found to be more available for hybridization compared to DNA-immobilized microstructured ZrO2/ERGNO. Therefore, ZrO2–ERGNO (obtained by a single step) could be more helpful than ZrO2/ERGNO for fabricating highly sensitive DNA sensors.

Also, Zuo et al.\cite{287} proposed a polishable, simple, and renewable DNA biosensor for DNA hybridization detection based on a ZrO2-modified carbon paste electrode. In this process, the paste was formed by mixing zirconia (19%) with graphite powder (56%) and paraffin wax (25%). The surface of the electrode was further attached by an oligonucleotide probe having terminal 5'-phosphate groups. This DNA sensor displayed high selectivity and sensitivity for differential pulse voltammetry (DPV) experiments.

The diversity and complexity of samples have imposed many restrictions for accurate and rapid semen identification to diagnose infertility in males. In 2019, Sun et al.\cite{288} introduced a novel colorimetric sensor for accurate and quick identification of human semen by coupling Zr-MOFs with ssDNA-decorated Au NPs (ssDNA–AuNPs) (Figure 15C). Zr6 clusters coordinately interact with the phosphate groups of DNA and also form

Figure 15. A) Proposed schematic for the fabrication of nano-ZrO2/ITO-based DNA biosensor. Reproduced with permission.\cite{285} Copyright 2009, Elsevier B.V. B) The DNA probes on the nanostructured ZrO2–ERGNO showing more accessibility than those on the microstructured ZrO2/ERGNO for DNA hybridization. Reproduced with permission.\cite{286} Copyright 2013, Elsevier B.V. C) Mechanism of the colorimetric sensor array strategy for semen sample detection. Reproduced with permission.\cite{288} Copyright 2019, American Chemical Society.
H bonding and π–π stacking. When the semen samples are added to the test solutions, the proteins or the other contents present in the samples affect the coprecipitation of ssDNA–AuNPs and Zr-MOFs. Successively, a color change of the supernatant occurs, resulting in the fabrication of a biosensor for human semen. Studies have also revealed that this method could also estimate the difference between infertile, healthy, and recurrent abortion cases.

Xiao et al.[289] proposed a novel platform for the immobilization of oligonucleotides over zirconia-modified filter paper. The oligonucleotide-functionalized zirconia-modified paper exhibited great sensitivity and generated a duplicate recognition effect of the targeted DNA at the nanoscale level. The metal oxide deposition on cellulose fibers enhanced the surface area for the immobilization. With the properties of degradability, nontoxicity, and flexibility, such biologically immobilized cellulosic materials could be a promising candidate for many practical fields such as immunoassay, separation, sensing, and biomolecular enrichment.

Yang et al.[290] showed that the alteration of the glassy carbon electrode surface with a single-walled carbon nanotube (SWNT)/2,6-pyridinedicarboxylic acid (PDC) composite enhanced the electrode surface’s activity. Electropolymerization of the carboxyl-group-functionalized SWNTs and PDC was conducted on the glassy-carbon electrode (GCE) surface to form SWNT/PDC composite films. Zirconia was electrodeposited on SWNTs/PDC/GCE and DNA probes were further immobilized on zirconia films due to the strong affinity of DNA phosphate groups toward zirconia. This DNA sensor was highly stable and straightforward in use. This method was efficient for PAT gene fragment detection.

### 7.3.3. Multimodel Zr-NS-Based Enzymatic Biosensors

Cai et al.[291] designed a graphene–chitosan–ZrO₂ composite for the immobilization of glucose oxidase (GOD) in the composite matrix. After immobilization, GOD retained its structure along with its electrocatalytic activity. The integrated graphene, chitosan, and ZrO₂ created a favorable environment for GOD and stimulated direct electron transfer at the surface of the electrode. Electrochemical studies revealed that the fabricated glucose biosensor has a low detection limit, high sensitivity, and excellent reproducibility. Furthermore, Vilian et al.[292] engineered a glucose biosensor by immobilizing GOD into a nanocomposite made from poly-(l-lysine) (PLL) and rGO–ZrO₂. The direct electrochemical studies of the GOD displayed fast electron-transfer constants and improved redox peak currents. The modified biocatalyst displayed tremendous electrocatalytic ability for the detection of glucose. The designed biosensor gave functional analytic parameters for the effective detection of glucose when detected by the DPV technique. Also, the biosensor exhibited excellent reproducibility, repeatability, and stability. Such composite films can also be tested for immobilization of distinct enzymes and proteins (Figure 16).

Hu et al.[293] designed a highly selective and sensitive DNA-sensing strategy to identify the existing point mutation in targeted DNA sequencing by combining a label-free hairpin probe with DNA endonuclease enzyme with ZrO₂ NPs (Figure 17A). This method resulted in a promising screening platform for detecting genetic diseases and infections and forensic and environmental applications.

Sumana et al.[294] designed a biosensor for the detection of urea by the coimmobilization of urease and glutamate dehydrogenase over ZrO₂ films deposited on gold-coated glass electrochemically...
The ZrO2/Au electrode displayed high sensitivity (0.071 μA mM⁻¹ cm⁻²) and linearity (100 mg dL⁻¹). Further, Srivastava et al. introduced the designing of a mediator-free microfluidics sensors with PDMS microchannels for the rapid sensing of urea (Figure 17C). The coimmobilization of Urs and glutamate dehydrogenase (GLDH) fabricated such a biosensor on a TiO2–ZrO2 nanocomposite. The designed mediator-free sensor exhibited enhanced detection limit, sensitivity, and faster response time to detect urea majorly due to the greater electrocatalytic behavior of the TiO2–ZrO2 nanocomposite and smaller sensor geometry. Also, the reproducibility of the bioelectrode was obtained at least 12 times. Such microfluidic devices could be further used to detect other analytes such as low-density lipoprotein and cholesterol.

Shukla et al. described the fabrication of a novel nanoplat-form in the form of a dendrimer-zirconia nanocomposite for the immobilization of urease enzyme. The response of the biosensor toward urea within 4 s displays the host-guest capability and biocompatibility of the poly(propylene imine) dendrimer. Photometric studies also showed that the urease enzyme retained its activity even after its immobilization. The urease enzyme also exhibited high reactivity after immobilization. Further, Chavhan et al. fabricated an efficient biosensor for the determination of vitamin C/ascorbic acid. The nano-ZrO2 films have been used for the immobilization of ascorbate oxidase obtained from Cucurbita species. The AsOx/nano-ZrO2/ITO electrode creates faster and direct electron transfer between the AsOx enzyme and the ITO electrode. Therefore, the AsOx/nano-ZrO2/ITO bioelectrode displayed enhanced biosensing parameters such as linearity, low detection limit, fast response time, and high sensitivity. These results could be attributed to the favorable orientation of ascorbate oxidase molecules in the nano-ZrO2 matrix.

Ahmad et al. fabricated a phenolic biosensor by immobilizing tyrosinase enzyme over zirconium oxide/polyethylene glycol composite film to estimate phenolic compounds. The described biosensor exhibited an ultrafast response time of less than 10 s, high sensitivity, and excellent storage stability of 30 days. Batra et al. engineered an improved amperometric bilirubin biosensor by immobilizing bilirubin oxidase, which is covalently bonded on a SiO2@ZrO NP hybrid attached to a gold electrode via chitosan film. The generated biosensor exhibited a rapid response of 2 s, a wide linear range from 0.02 to 250 mM, a lower detection limit of 0.2 nM, high stability of 4 months, and excellent reproducibility.

Pundir designed a choline-based biosensor by immobilizing two enzymes—acetylcholinesterase (AChE) and choline

(Figure 17B). The ZrO2/Au electrode displayed high sensitivity (0.071 μA mM⁻¹ cm⁻²) and linearity (100 mg dL⁻¹). Further, Srivastava et al. introduced the designing of a mediator-free microfluidics sensors with PDMS microchannels for the rapid sensing of urea (Figure 17C). The coimmobilization of Urs and glutamate dehydrogenase (GLDH) fabricated such a biosensor on a TiO2–ZrO2 nanocomposite. The designed mediator-free sensor exhibited enhanced detection limit, sensitivity, and faster response time to detect urea majorly due to the greater electrocatalytic behavior of the TiO2–ZrO2 nanocomposite and smaller sensor geometry. Also, the reproducibility of the bioelectrode was obtained at least 12 times. Such microfluidic devices could be further used to detect other analytes such as low-density lipoprotein and cholesterol.

Shukla et al. described the fabrication of a novel nanoplat-form in the form of a dendrimer-zirconia nanocomposite for the immobilization of the urease enzyme. The response of the biosensor toward urea within 4 s displays the host-guest capability and biocompatibility of the poly(propylene imine) dendrimer. Photometric studies also showed that the urease enzyme retained its activity even after its immobilization. The urease enzyme also exhibited high reactivity after immobilization. Further, Chavhan et al. fabricated an efficient biosensor for the determination of vitamin C/ascorbic acid. The nano-ZrO2 films have been used for the immobilization of ascorbate oxidase obtained from Cucurbita species. The AsOx/nano-ZrO2/ITO electrode creates faster and direct electron transfer between the AsOx enzyme and the ITO electrode. Therefore, the AsOx/nano-ZrO2/ITO bioelectrode displayed enhanced biosensing parameters such as linearity, low detection limit, fast response time, and high sensitivity. These results could be attributed to the favorable orientation of ascorbate oxidase molecules in the nano-ZrO2 matrix.

Ahmad et al. fabricated a phenolic biosensor by immobilizing tyrosinase enzyme over zirconium oxide/polyethylene glycol composite film to estimate phenolic compounds. The designed biosensor exhibited an ultrafast response time of less than 10 s, high sensitivity, and excellent storage stability of 30 days. Batra et al. engineered an improved amperometric bilirubin biosensor by immobilizing bilirubin oxidase, which is covalently bonded on a SiO2@ZrO NP hybrid attached to a gold electrode via chitosan film. The generated biosensor exhibited a rapid response of 2 s, a wide linear range from 0.02 to 250 mM, a lower detection limit of 0.2 nM, high stability of 4 months, and excellent reproducibility.

Pundir designed a choline-based biosensor by immobilizing two enzymes—acetylcholinesterase (AChE) and choline
oxidase (ChO), over a c-MWCNTs/ZrO2 NP nanocomposite electrodeposited on GCE. The designed AChE–ChO–c-MWCNT/ZrO2 NP/GCE bioelectrode exhibited response time of 4 s, detection limit of 0.01 μM, and working range from 0.05 to 200 μM, respectively. The electrode displayed 60 days as half-life at 4 °C.

Zong et al.\cite{301} proposed designing a biocompatible, novel, nontoxic, and thermally steady ZrO2-grafted collagen trihelix scaffold fabricated on a graphite electrode. Such scaffolds provided a favorable microenvironment for biomolecule loading and assisted them in retaining their natural structures. The ZrO2-grafted collagen trihelix scaffold was immobilized by horseradish peroxidase (HRP) enzyme. This scaffold enhanced the electron transfer on HRP, resulting in direct electrochemical behavior with excellent thermal stability till 80 °C. The HRP-immobilized ZrO2-grafted collagen displayed a great electrocatalytic activity toward the reduction of H2O2 without any mediator. Such a grafted biosensor would provide an excellent platform for the immobilization of proteins. Furthermore, Tong et al.\cite{302} derived a novel biosensor by immobilizing the HRP enzyme over DNA/ZrO2/modified Au electrode. Attachment of DNA via the 5′ end to ZrO2 developed a favorable microenvironment for the biomolecules’ immobilization. It also enhanced the electron transfer between the electrode surface and the HRP enzyme.

Wang et al.\cite{303} engineered a ZrO2 adsorption-based immunodassay through electrochemical quartz crystal microbalance (EQCM) for the recognition of phosphorylated acetylcholinesterase (phospho-AChE) as a novel biomarker for the monitoring organophosphate (OP) exposures (Figure 17D). The zirconia films derived by the electrodeposition method using a hydroxyl-derivatized monolayer as a template were used for selective capture of phosphoryl-AChE from media. Further, HRP-labeled anti-AChE antibodies were immobilized for the detection of captured phosphorylated proteins. The HRP catalyzes the H2O2 oxidation of the benzidine substrate, resulting in the insoluble product over the functionalized crystal.

### 7.3.4. Other Biosensing Applications of Multimodel Zr-NSs

Chen et al.\cite{304} designed a novel approach for the fabrication of an electrochemical biosensor to evaluate the protein kinase activity (PKA) (Figure 18A). In this study, a rGO–ZrO2–thionine nanocomposite efficiently functioning as a phosphopeptide-recognizing, signal-amplifying and reporting platform. The thionine conjugates with the rGO surface via π bonding. The designed nanocomposite exhibited a one-step and label-free electrochemical evaluation of kemptide phosphorylation by PKA. The reported detection limit for PKA by rGO–ZrO2–thionine nanocomposite is 0.005 U mL−1, lower than previously known methods. This method was also proposed for the accurate evaluation of inhibitors. Therefore, the rGO–ZrO2–thionine nanocomposite provides an excellent route for sensitive and generic electrochemical assay of inhibitors and protein kinase activities. Sun et al.\cite{305} designed a facile and efficient method for preparing ZrO2–CNT nanocomposites (Figure 18B). The entire outer region of CNTs was covered by uniform amorphous ZrO2. The designed nanocomposite exhibited higher selectivity and sensitivity toward ethanol via chemiluminescent detection. Shahamirifard et al.\cite{306} designed an ultrasensitive electrochemical sensor (ZrO2–ChCl–AuNPs/CPE) for simultaneous determination of gallic acid and uric acid. Such modified electrodes displayed higher electrocatalytic activity, sensitivity, and selectivity for GA and UA. However, the electrode displayed lesser performance in basic media. The designed sensor could be used for GA and UA detection in pharmaceutical, horticultural practice, food and biological analyses, and other industries.

Venu et al.\cite{307} designed an ultrasensitive electrochemical sensor for an anticancer drug (regorafenib, REG). In this study, a ZrO2/rGO composite was prepared for evaluation. The rGO support enhanced the electrocatalytic performance of ZrO2 toward an REG anticancer drug. The ZrO2/rGO/GCE was applicable for the determination of REG in the presence of ascorbic acid and uric acid. Therefore, such an electrochemical sensor has a promising future for ultrafast detection of various anticancer drugs in human blood serum and other pharmaceutical formulations.

### 7.4. Other Promising High-Performance Applications of Multimodel Zr-NSs

Apart from the outstanding applications in dentistry, bone implantation, and biosensors, zirconia NPs are also recognized for various other applications. Some of the other applications are listed subsequently.

#### 7.4.1. Photocatalytic Applications of Multimodel Zr-NSs

With the increasing worries about future energy sources, researchers proposed new materials for sunlight harvesting. ZrO2 is not considered a promising material for sunlight absorption because zirconia acts as a semiconductor with a wide bandgap (5 eV) capable of absorbing UV light only. Sinhamahapatra et al.\cite{308} fabricated oxygen-deficient black zirconia (ZrO2-x) using the magnetothermic reduction method in a H2/Ar atmosphere, with decreased bandgap (1.5 eV) and increased solar light absorption. A notable surface alteration as disorders or defects linked with the oxygen vacancy occurs in the black zirconia when fabricated by the aforementioned method. Oxygen-deficient ZrO2-x displays outstanding photocatalytic RhB degradation performance and H2 production under simulated solar light. Such a black ZrO2-x material could be a promising alternative for photocatalytic applications and other applications, such as solar applications, catalysis, energy conversion and storage, sensors, coatings, and other biomedical applications.

#### 7.4.2. Catalytic Applications of Multimodel Zr-NSs

Ehrlich et al.\cite{309} used chitosan scaffolds excreted from *Aplysia cauliformis* (marine sponge) as the template for the novel in vitro fabrication of ZrO2 NPs by using the hydrothermal method. The stability of the chitosan 3D matrix toward extreme conditions makes it an ideal template for the hydrothermal synthesis of ZrO2 NPs. The designed zirconium–chitin composite executes applications in multiple fields such as synthetic catalysis, dentistry, and as a bone replacement material. Yang et al.\cite{310} successfully assembled small-molecular phytic acid (PA) with ZrO2 NPs in layer-by-layer [PA/ZrO2]n films over solid surfaces. The designed films tend to adsorb or load myoglobin (Mb) into the films when immersed in Mb solutions. The [PA/ZrO2]n–Mb
films at pyrolytic graphite electrodes exhibited a quasi-reversible and well-defined cyclic voltammetry (CV)-response myoglobin–Fe$^{3+}$/Fe$^{2+}$ redox couple. The material also demonstrated excellent electrocatalytic properties toward hydrogen peroxide and oxygen. This study explored the interaction among [PA/ZrO$_2$]$_n$ films and Mb molecules and the driving force responsible for the film assembly. The driving force responsible for forming [PA/ZrO$_2$]$_n$ multilayer films is the coordination interaction between ZrO$_2$ and PA. The electrostatic attractions present between the film components and the oppositely charged Mb are the significant interactions for the Mb loading.

Kaminski et al.\textsuperscript{[311]} proposed a novel approach for synthesizing mesoporous ceria, zirconia, and cerium–zirconium oxides that could be used as supports for designing monometallic and bimetallic (copper and gold) catalysts. The designed materials were tested for the oxidation of glycerol in a basic aqueous medium and to detect the presence of molecular oxygen. A negative charge generated on the gold species and the amount of Cu$^+$ increased over the catalyst surface due to the interactions between the copper and gold species in bimetallic samples. Such interactions increase the catalytic oxidation of glycerol displayed by bimetallic catalysts compared to monometallic samples. Bimetallic catalysts exhibited excellent selectivity toward glyceric acid (GLA).

7.4.3. Gas-Sensing Application of Multimodal Zr-NSs

Emission gases have always attracted the attention of researchers as they consist of the leading greenhouse gases that cause air pollution. Nitrogen oxide (NO$_x$) exhaust gas sensors could play a vital role in regulating engine operations and monitoring diesel emissions. Sensors with efficiency, accuracy, and greater sensitivity could be very useful in monitoring air pollution and fulfill
future emission requirements. Recently, Killa et al.\cite{312} presented the interpretation of the reactions governing NO\textsubscript{x} gas sensing by porous stabilized ZrO\textsubscript{2}-based sensors. The results showed a strong dependency on sensor porosity, and higher activation energies were obtained for materials with higher porosity. DMello et al.\cite{313} designed and synthesized Zr–NH\textsubscript{2}–benzenedi-carboxylate MOF and thereafter successfully used its role as an excellent chemiresistive sensor for the detection of various acidic gases. The designed MOF displayed robust and rapid sensing ability toward SO\textsubscript{2}, CO\textsubscript{2}, and NO\textsubscript{2} at lower concentrations.

7.4.4. Fluorescence Resonance Energy Transfer (FRET) Bioprobe Supported by Multimodel Zr-NSs

Modified-zirconia NPs have also shown their applications as FRET bioprobes to selectively detect avidin and specific recognition of cancer cells. Recently, Liu et al.\cite{298} introduced novel inorganic oxide biolabel, amine-functionalized tetragonal ZrO\textsubscript{2}–Ln\textsuperscript{3+} NPs (Figure 19). They have also introduced a new bioconjugate method for quantitative bioconjugation among the designed material and varied biomolecules such as biotin and amino-terminal fragment (ATF). The long-lived luminescence and optical properties of Ln\textsuperscript{3+} were utilized for demonstrating the application of designed amine-functionalized lanthanide-doped zirconia NPs as an effective TR-FRET bioprobe for the selective sensing of avidin with a lower limit of detection. ZrO\textsubscript{2}–Tb NPs further bioconjugate with ATF of a urokinase plasminogen activator to exhibit specific recognition ability for cancer cells.

7.4.5. Phosphatase Mimetic Activity of Multimodel Zr-NSs

Hu et al.\cite{314} demonstrated the phosphatase mimetic activity of ZrO\textsubscript{2} NPs (Figure 20). It was substantiated that ZrO\textsubscript{2} NPs exhibited excellent catalytic activity toward the dephosphorylation of chromogenic and fluorogenic substrates of natural phosphatases. ZrO\textsubscript{2} NPs also showed activity toward essential biomolecules such as catalyzing the dephosphorylation of o-phospho-L-tyrosine and ATP but remained unreacting with DNA strands. Also, ZrO\textsubscript{2} NPs illustrated potential application in intracellular imaging.

7.4.6. Lubricant Oil Additives of Multimodel Zr-NSs

Zirconia nanocomposites have also exposed their applications as lubricant oil additives. Zhou et al.\cite{315} proposed a successful one-pot hydrothermal synthesis of a uniformly distributed rGO/ZrO\textsubscript{2} nanocomposite. The rGO/ZrO\textsubscript{2} nanocomposite was tested as a lubricant oil additive and exhibited excellent dispersion stability in paraffin oil and displayed excellent antiwear and friction-reduction properties. ZrO\textsubscript{2} acts as a spacer preventing the restacking of rGO nanosheets. It was concluded from the results that the rGO/ZrO\textsubscript{2} nanocomposite could be used as lubricant additives for enhancing the tribological properties of lubricants. Devadas et al.\cite{316} reported the ZrO\textsubscript{2} NPs’ incorporation within functionalized MWCNTs and applied the nanocomposite to detect p-nitrophenol in aqueous samples.

8. Challenges Associated with Multimodel Zr-NSs

As discussed in previous sections, to avoid fractures during cooling after the sintering process at elevated temperatures, zirconia is doped with oxides. Doping of zirconia with oxides and reduction in the tetragonal monoclinic transformation temperature could lead to the stabilization of the tetragonal phase to a certain extent only, making zirconia useful as a structural bulk material. However, even after doping oxides in zirconia, the tetragonal phase remains metastable. Garvie et al.\cite{317} and Gupta et al.\cite{318} reported that zirconia undergoes transformation toughening due to disruptive phase transitions that display resistance toward crack propagation. The stress-induced phase

![Figure 19](https://example.com/figure19.png)  
**Figure 19.** A) Schematic illustration displaying the specific recognition of ZrO\textsubscript{2}–Tb-ATF NPs to H1299 cancer cells with uPAR high expression. B) Confocal laser scanning microscopy (CLSM) images of (a) H1299 and (b) HELF cells after incubation with ZrO\textsubscript{2}–Tb-ATF NPs (1 mg mL\textsuperscript{-1}) for 2 h at 37 °C. Tb green emissions are shown in panel 1 (λ\textsubscript{em} = 500–560 nm, λ\textsubscript{ex} = 488 nm). DAPI blue images (λ\textsubscript{em} = 450–490 nm, λ\textsubscript{ex} = 405 nm) that indicate the nuclear regions are shown in panel 2. Panel 3 is the bright-field image that outlines the position of cells, and panel 4 is the overlay image of panels 1, 2, and 3 (scale bar = 30 μm). C) In vitro dark cytotoxicity and phototoxicity of ATF-coupled ZrO\textsubscript{2}–Tb NPs against HELF cells after 4 h incubation. Reproduced with permission.\cite{340} Copyright 2012, American Chemical Society.
transformation includes converting the metastable tetragonal phase into a monoclinic phase, accompanied by the volumetric expansion and induction of compressive stresses. Even after stabilizing with stabilizing oxides, Zr-NSs must face various challenges. In this part of the Review, the challenges associated with Zr-NSs are briefly overviewed.

8.1. Low-Temperature Degradation of Zr-NSs

One of the significant challenges faced by Zr-NSs is low-temperature degradation. YSZ ceramics, members of the toughened material family, tend to display bending strength greater than 1000 MPa and toughness approximately lying within 5–10 MPa m^{1/2}. Due to such extraordinary features, in the late 1980s, YSZ attained massive popularity for manufacturing femoral heads. At that time, YSZ was chosen over the other ceramics due to its extraordinary balance between strength and toughness. Till date, above 600,000 femoral heads made of zirconia have been implanted globally, especially in Europe and the United States. But Kobayashi et al.'s findings dampened the excitement developed by these ceramic materials. Kobayashi et al. discovered a severe limitation of YSZ, initially for applications near the temperature 250 °C. This study discovered that YSZ ceramics might suffer from a slow t-to-m phase transformation at the surface of the sample in a humid atmosphere, resulting in the generation of microcracks and degradation in strength. After this discovery, a chain of publications was attempted to evaluate the elementary mechanisms of the slow t-to-m transformation and minimize this limitation phenomenon. This t-to-m transformation phenomenon is often entitled as low-temperature degradation (LTD) or aging.

Even after vast continuous research worldwide, the mechanisms underlying the aforementioned phenomenon have not yet been confirmed. The rise in internal stresses is probably due to the penetration of water species inside the lattice, which initiate the transformation. This is followed by the occurrence of a cascade of actions, the propagation of the transformation first inside the grain and then conquering the surface of the sample and the core by the nucleation and growth mechanism of severe treatments. Recently, Chevalier et al. described the various sequences and processes of aging in a critical review. The aging process mainly occurs due to the water-assisted martensitic transformation, which via propagating at the surface invades the whole bulk. The aging process generally results in microcracking and roughening. In the hip joint heads, LTD resulted in enhanced wear and further release of the wear debris into the body. Moreover, in extreme cases, it resulted in the catastrophe of the material. Many upgraded technologies have been designed to monitor and predict the LTD before surgery. Novel zirconia and zirconia-based...
composites have been introduced to deal with significant shortcomings of the ordinary YSZ.

As stated previously, to date, no mechanism explains the LTD phenomenon but only provides speculations. Among all the accepted mechanisms, the soundest ones are as follows. 1) Lange et al.[326] carried out some TEM observations, and proposed water molecules react with yttria to form $\text{Y(OH)}_3$-rich clusters, resulting in reducing the stabilizer oxides into the surrounding, making zirconia grains free to transform into the monoclinic phase. 2) Yoshimura et al.[323] suggested that the Zr─O bond in zirconia is attacked by water vapor, leading to the breakage of the bond, and ultimately results in the accumulation of stress due to the movement of $\text{OH}$, which in turn produces lattice defects behaving as nucleating agents for transformation. 3) Chevalier et al.[325] proposed that the $\text{O}^{2-}$ formed from the water dissociation might be solely responsible for filling the oxygen vacancies, which are supposed to be the reason for destabilization and LTD.

Even if the mechanism is not specific, it is well recognized that the phase transformation initiates from the sample surface, then proceeds inward, causes surface uplift and microcracks along with aesthetic degradation, opens the water penetrating possibility beneath the surface, and therefore propagates the transformation into the sample interior, finally resulting in the growth of significant cracks.[327–329]

The ageing process could have long-term consequences on the performance of zirconia implants, such as the ageing process being linked with microcracking and roughening. This will unavoidably affect the hip joint heads' wear performance because the wear rate is enhanced due to the roughening process. However, the combined effect of wear and surface microcracking will lead to zirconia grain pullout. Due to the pullout of small particles, these particles interact with the immune system cells critically. It is also proposed that these particles enter inside the periprosthetic tissues after their generation at the contact surfaces and thereafter trigger the macrophages for further reactions. These macrophages then further release proinflammatory cytokines, which tend to stimulate osteoclastic bone resorption, causing osteolysis, ultimately propagating the transformation into the microcracked transformed zone results in the generation of defects. As zirconia is very much prone to slow crack growth due to stress corrosion, the implant fracture is inescapable and is applicable to both orthopedic and dental devices.[325]

Guo et al.[330] proposed a novel low-temperature degradation mechanism for tetragonal zirconia ceramics in water, based on the assumption that degradation is accomplished via the annihilation of the oxygen vacancies in the lattice of zirconia, and propagation occurs along the grain boundaries. According to the study, oxygen vacancies play a decisive role in the degradation phenomenon. Furthermore, Hallmann et al.[331] evaluated the effect of GS and air abrasion on the LTD of YSZ. In this study, sintering of disc-shaped specimens was done at 1350, 1450, and 1600 °C, and air abrasion was accomplished using distinct abrasive particles. After storing the specimens at 134 °C for 2 h, the specimens were characterized. The YSZ specimen sintered at 1350 °C did not suffer the tetragonal-to-monoclinic phase conversion while accelerating aging. The diffusion-controlled transformation got initiated when the sintered temperature was 1450 °C, and the transformation was noteworthy when the sintered temperature was 1600 °C. The study confirmed that the degradation of YSZ at accelerated aging conditions depends strongly on the GSs. When the critical value of the GS (0.3 μm) is achieved, the transformation occurs. The highest degradation rate was observed when the sintering temperature was 1600 °C, and the average GS was 0.72 μm. The study also illustrated that the cracks and flaws generated on the YSZ surface by the air abrasion process did not play an essential role in the LTD process. The airborne particle size was not the fundamental reason for the LTD. The LTD retardation due to air abrasion was witnessed for specimens sintered at 1600 °C. No formation of the Zr─OH and Y─OH bonds was detected. The study claimed that a stable YSZ could be acquired when the sintering temperature varies between 1350 and 1450 °C.

Inokoshi et al.[332] also investigated the influence of sintering parameters on LTD of zirconia ceramics and reported that the higher sintering temperature and extended dwelling times enhanced the GS of zirconia. Similarly, a higher amount of ZrO$_2$ grains attained cubic crystal structures, leading to decreased yttria content in the rest of the t-grains. The developed conditions of bigger GSs and lesser content of stabilizer made the zirconia tetragonal grains more susceptible to LTD.

Moreover, Hallmann et al.[333] evaluated the effect of sintering temperature and dopants on the microstructure and LTD of Y-TZP zirconia. The results validated that a faster ageing occurred at 134 °C under 2.3 bar water vapor pressure for 2 h. It was also observed that the average GS increased with the increase in sintering temperature. The average GSs were <0.3 μm at 1350 and 1400 °C but the average sizes were larger when the temperature was further increased. Therefore, the dopant and GS adversely influenced the stability of the tetragonal phase under LTD conditions. Also, Y-TZP ceramics with GS > 0.3 μm were found to be unstable under LTD conditions and cannot be used for a longer time in a moist environment.

From the previously reported evidence, various guidelines can be established to assess the design constraints. LTD happens in pure ZrO$_2$ stabilized with Y$_2$O$_3$ (2.5 mol%) and in Al$_2$O$_3$/ZrO$_2$ samples with ZrO$_2$ stabilized with Y$_2$O$_3$ (2.5 mol%) and CeO$_2$ (8.5 mol%). When the tensile stresses are of the magnitude of a few hundred megapascals, the samples are more prone to long-term LTD. LTD also occurs when in mixed Al$_2$O$_3$/ZrO$_2$ samples, ZrO$_2$ is in microscopic tension compared to pure ZrO$_2$ subjected toward macroscopic tensile stresses. Also, when the GS is of the magnitude 300 nm, the ZrO$_2$ samples might exhibit LTD after a few years. Also, all this evidence points toward the fact that the transformation (t→m) takes place initially over the surface and then penetrates underneath. Water vapors also contribute to accelerating the LTD. In a critical review, Lughri and Sergio[334] presented engineering guidelines for employing zirconia-based materials in dentistry, which are based on previously reported conclusions. According to these guidelines, the density must be greater than 99%, the content of stabilizer (Y$_2$O$_3$) should be between 3.5 and 8 mol%, GS must be lesser than 0.3 μm, residual stress must be lower than 300 MPa, and the strength in four-point bending initially and after ageing testing must be 600 MPa.
8.2. Issue of Catastrophic Fracture with Zr-NSs

As discussed in previous sections, zirconia and zirconia-based composites have exhibited outstanding applications in dentistry and medicine attributed to their beneficial biological, physical, corrosion, and esthetic properties. Orthopedic hip replacements by zirconia have presented superior resistance to wear over other systems. But the jeopardy of catastrophic fracture remained a significant concern. As stated earlier, the tetragonal or cubic phase of the zirconia lattice relapses into the monoclinic phase and further expands on ambient temperature cooling. However, significant stresses are also generated in the zirconia lattice upon cooling. The lattice becomes very hard and incapable of accommodating the associated expansion. Such internal stresses can either lead to catastrophic fracture or endorse the residual stresses to inspire crack propagation with time. The transformation of the t-phase into the m-phase is a foremost issue in dental restorations, in which ceramic prosthesis is custom fired to form the final structure. Cooling of such structures would undoubtedly lead to catastrophic fractures, earlier or later. In orthopedic applications, the crack propagation and residual stresses would result in prosthesis failure, mostly with considerable morbidity. To evaluate the catastrophic fracture and resolve this issue, many studies have been reported in the last few years.

Salameh et al.\[335\] conducted experiments to examine the effect of fiber posts on the fracture resistance of zirconia crowns implanted above endodontically treated mandibular molar teeth with a distinct coronal damage level. Statistical scrutiny declared that specimens comprising fiber posts displayed considerably greater failure loads and favorable fracture patterns than the controls. At the fractographic investigation, the specimens with fiber posts illustrated the veneer ceramic’s delamination from intact ZrO\(_2\). In the meantime, the specimens without fiber posts displayed microcracking leading to the damage of the support beneath the ZrO\(_2\) crowns, which was the reason for the beginning of radial cracks and catastrophic damages. With the limitations, the implantation of the fiber posts improved the zirconia crown supports, resulting in higher fracture loads.

Further, Sulaiman et al.\[336\] examined the effect of catastrophic fracture on the failure rates of monolithic ZrO\(_2\) restorations by conducting clinical performance over 5 years. The group collected data from commercial dental laboratories for over 5 years. Around 39 827 restoration records were accessed, which involved 3731 anterior restorations (1952 single crowns (SCs) and 1799 fixed dental prostheses (FDPs)) and 36 096 posterior restorations (6288 FDPs and 29 808 SCs). The complete fracture rate for all the restorations up to 5 years was recorded as 1.09%. Fracture rates for anterior and posterior restorations were reported as 2.06% and 0.99%, respectively. Moreover, the reported fracture rates for anterior SCs and posterior SCs were 0.97% and 0.69%, respectively, whereas the combined rate for anterior and posterior was 0.71%. In FDPs, the fracture rates were evaluated as 3.26% and 2.42% for anterior and posterior, respectively, and the combined rate was 2.60%. The short-term 5-year analysis concluded that restorations fabricated from the monolithic zirconia exhibited comparatively lower fracture rates. Anterior restorations displayed a slightly greater fracture rate than posterior restorations, and FDPs exhibited two times the rate of SCs.

Recently, Chen et al.\[337\] evaluated the fracture behavior of yttria and lanthanum codoped zirconia fabricated via the microwave hybrid sintering route. The study displayed that the average toughness values of conventional and microwave-sintered samples (1550 °C) were 4.31 and 7.68 MPa m\(^{1/2}\), respectively. The average grain size obtained from the microwave sintering method (500 nm) was lesser than that of the conventional one (700 nm). The microstructures obtained from the fracture samples displayed that the intergranular fractures were core structures for microwave-sintered specimens, whereas various transgranular fractures were critical features in conventionally sintered specimens. The XRD results disclosed that the content of monoclinic phase progressively increased as the microwave sintering temperature increased. The study also proposed that under the influence of the microwave effect, the induced phase transformation and the grain boundary diffusion collectively weakened the grain boundary bonding strength.

9. Conclusion

In a few decades, zirconia nanostructures have emerged as an excellent platform with numerous applications in the biomedical field. Zirconia’s superficial biocompatibility, low corrosion potential, and superior mechanical strength have made it a sustainable substitution for conventionally used orthopedic joint replacement materials. One of the foremost benefits of zirconia’s femoral head and bearing structures is comparatively lower wear rates than those of conventionally used alloy-head/polymethylene-bearing liners. Such unique characteristics increase the hip replacement’s life expectancy, which is predominantly advantageous for younger and long-term-survival patients who get such invasive implants in a substantial morbidity procedure. However, regardless of the aforementioned benefits, zirconia is brittle and prone to crack propagation and aging degradation. The tetragonal–to-monoclinic form transformation might be triggered due to the presence of water, repetitive loading, and higher temperatures, leading to the weakening of zirconia’s mechanical strength. Many catastrophic failures of femoral heads made of zirconia have been credited to this mechanism. The risk of femoral head fracture has been reduced with the improved understanding of the material characteristics and sintering process development. The catastrophic fracture restricts the all-round approval of ceramic joint components (Figure 21).

However, novel biomaterials, for instance, ZTA, are under continuous advancement and require further clinical evaluation to evaluate the long-term performance and reliability. The most significant measure of victory is the long-term clinical performance of designed Zr-NSs. The development of zirconia dental implants could be a promising alternative for those patients who suffer from true titanium allergy or want a metal-free replacement. Since 2004, implants made from zirconia have become commercially available, especially in Europe. In 2016, the very first zirconia-based implant was launched by one of the leading implant manufacturers in the United States. The request for ceramic implants is anticipated to remain increasing due to more awareness of patients’ health and esthetics. Moreover, due to the
limited amount of clinical testing with comparatively short observation durations offered, additional examinations on the long-term performance of zirconia implantations are significantly required beforehand for the universal approval of such treatment options.

The hip replacement procedure has become a predictable and standard orthopedic procedure. The success rate of this procedure is quite remarkable, although the average life expectancy of a conventionally used alloy–polymer hip implant is limited to only 20–30 years. Such a low life expectancy is not sufficient for all patients, especially for younger patients expecting a relatively long lifespan. Zirconia femoral head–bearing systems have been designed to improve the life expectancy of hip implants by means of zirconia’s excellent wear resistance. Due to the risk of catastrophic failures and deficiency of long-term clinical records, zirconia hip implants have not yet been recognized in North America. Until records become accessible and technological developments for ceramics evolution, zirconia hip implantations are not considered the best choice for a vast number of patients, and will possibly remain as an alternative for younger patients. In view of current ongoing trends toward lesser invasive dental restorations, it is noteworthy that monolithic zirconia will surely overrule the dental restorations in the next few years. In the biosensing field, various Zr-NSs have already contributed a significant part in various applications. The enhanced beneficial properties of Zr-NSs suggest that future research is likely to lead toward the development of new types of biosensors. Presently, researchers are focusing on investigating the mechanism of numerous biomolecule–transducer interactions using these fascinating nanostructures. Extremely sensitive biodetection protocols based on Zr-NSs successfully open the possibilities of crafting biosensors as disease markers. Enzyme-, DNA-, and antibody-based bioassays on Zr-NS platforms are also approximated to be applicable for multianalyte detection. In the future, innumerable novel Zr-NSs are expected to expand and evolve the biosensing area along with other biomedical fields.

Acknowledgements
G.R. and G.B. contributed equally to this work. The authors acknowledge their respective affiliated departments and institutions for providing support and facilities to complete this article. Y.K.M. acknowledges funding by Interreg Deutschland-Denmark with money from the European Regional Development Fund, project number 096-1.1-18 (Access and Acceleration).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
bioceramics, biomedical applications, functional materials, smart materials, zirconia

Received: March 16, 2021
Revised: May 5, 2021
Published online:

[1] J. A. Rodríguez, M. Fernández-García, Synthesis, Properties, and Applications of Oxide Nanomaterials, John Wiley and Sons 2006.
[2] C. Liang, X. Zhang, Z. Cheng, M. Yang, W. Huang, X. Dong, View 2020, 1, 20200046.
[3] V. Vedarethinam, L. Huang, M. Zhang, H. Su, H. Hu, H. Xia, Y. Liu, B. Wu, X. Wan, J. Shen, L. Xu, W. Liu, J. Ma, K. Qian, Adv. Funct. Mater. 2020, 30, 2002791.
[4] C. Pei, C. Liu, Y. Wang, D. Cheng, R. Li, W. Shu, C. Zhang, W. Hu, A. Jin, Y. Yang, J. Wan, Angew. Chem., Int. Ed. 2020, 59, 10831.
Garima Rathee received her Ph.D. degree from the Department of Chemistry, University of Delhi. She is a young researcher, who is currently exploring the applications of nanomaterials for environmental remediation, sensing, biosensing, catalytic organic transformations, and energy storage devices. She has designed multitasking novel ternary-layered double hydroxides and their respective nanocomposites and tested their applicability in distinct fields. She is open for collaborative research in her research interests, including designing of novel nanomaterials and their applications in the fields of catalysis, environment remediation, energy storage devices, and sensing as well as biosensing.

Gaurav Bartwal obtained his doctoral degree in organic chemistry from the University of Delhi. The unifying theme of his Ph.D. research work was to design and synthesize low-molecular-weight fluorescent probes (LMFPs) targeting environmental pollutants. He applied his organic chemistry skills to develop sustainable synthetic methodologies for the construction of pharmacologically relevant heterocycles and explored the catalytic role of nickel boride in various organic synthetic transformations. He is very keen to pursue research as his career, and is currently working on a project aimed at developing peptide-based multifunctional nanoplatforms targeting selective removal of organic micropollutants from water.

Jyotsna Rathee is currently working as an assistant professor at Maharaja Surajmal College and pursuing her Ph.D. degree from Deenbandhu Chhotu Ram University of Science and Technology. She has also worked as a senior project assistant at the Industrial Research and Development Unit, Indian Institute of Technology (IIT) Delhi, India, on accessible devices/concepts for the visually impaired. She is the winner of a national-level design competition. She has been working on implementing design ideas for impaired and differently-abled individuals. She has a strong hold on database, computer graphics, and IOT, having published papers on the same in recognized journals.

Yogendra Kumar Mishra is Professor MSO and Leader of the Smart Materials group at Mads Clausen Institute, University of Southern Denmark (SDU), Sønderborg, Denmark. He introduced a new flame-based process for metal oxide nanostructuring in complex 3D tetrapodal network form. These networks are useful for sacrificial templates to create hybrid and new 3D architecture materials. These tetrapodal materials have opened many new application avenues in physics, chemistry, engineering, health care, biomedicine, agriculture, water, environmental, and many other advanced technologies. At SDU, NanoSYD, the Smart Materials group's focus is to develop a new class of functional materials for sustainable technologies.
Ajeet Kaushik, Fellow-ICS, is working as an assistant professor of chemistry at Florida Polytechnic University and exploring nano-biotechnology for health wellness. He is an accomplished scientist (supported by publications, journal editors, edited books, patents, international collaborations) and the recipient of several international awards in support of his credentials. He is open for collaborative research. His research interests include nano-biotechnology, analytical systems, design and development of nanostructures and nanocarriers for drug delivery, nanotherapeutics for central nervous system diseases, on-demand site-specific release of therapeutic agents, exploring personalized nanomedicines, biosensors, point-of-care sensing devices, and related areas of healthcare monitoring.

Pratima R. Solanki is an assistant professor at the Special Centre for Nanoscience at Jawaharlal Nehru University, New Delhi. She is actively engaged in the research and development of biosensors utilizing nanostructured materials for health care and environmental monitoring. She is open for collaborative research at national and International level. Her research interests include nano-biosensing, design and development of nanostructures, electronic devices, toxin detection, and point-of-care devices. She received the fifth Visitor Award 2019 from the President of India for development of a biosensing platform for cancer biomarker detection.