

Zirconium Nanoparticles It's Biological Synthesis and Biomedical Application: A Review

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Abstract: Nanotechnology is starting with the characterization, fabrication, and possible applications of numerous materials at the Nano-scale. Over the last few eras, nanomaterials provide a platform for researchers from diverse arenas due to the high surface-to-volume ratio and other novelties, and new significant belongings. In Nanobiotechnology development of eco-friendly and reliable Synthesis of nanoparticles are important, but the development of a crucial method for the preparation of nanoparticles is very important. Apart from other nanoparticles zirconia nanoparticles are biocompatible; having mechanical, electrical, and optical properties draws much attention from the researcher. Different natural Phyto constituents exist in plant extracts such as polysaccharides, proteins, polyphenols, enzymes, vitamins, and steroids are responsible for the formation and stabilization of zirconium dioxide nanoparticles. Zirconium nanoparticles are receiving diverse biomedical applications because of their distinctive antimicrobial, antioxidant, anticancer, antifungal, antileishmanial, antilarvicidal, wound healing, anticholinergic, and anti-diabetic properties. In the last decades, different approaches are used for developing eco-friendly and safe approaches for the preparation of zirconium nanoparticles and avoiding hazardous by-products. In this review, we will focus on the biological preparation of zirconium nanoparticles and their diverse biomedical applications.

Keywords: Zirconium Nanoparticles, Biological Synthesis, Biomedical Applications

1. Introduction

Last year's nanotechnology is developing tremendously and is one of the fascinating branches of science [1, 2] because of its high demand and also its interesting applications in different fields which includes textile industries, food technology, health care, mechanics, electrochemistry, sensors, biomedicine, synthetics chemistry, cosmetics, catalysis, space industry, agriculture, pharmaceuticals, optics, and space industry [3]. As nanoparticles have various applications zirconium dioxide nanoparticles have numerous applications in various fields and got much attention from the researcher because of their valuable and unique characteristics which include catalytic, sensing, mechanical, thermal, electrical, biocompatible, and

optical characteristics and due to these characteristics ZrO₂ NPs are utilizing in various bone implants [4] solar cells, gas sensor, fuel cell, seed germination, photo-catalysis, refractory and energy [3]. Besides this due to their unusual physicochemical properties zirconium dioxide nanoparticles possess excellent anticancer, antifungal, antibacterial, and antioxidant properties [5, 6]. Usually, zirconium dioxide nanoparticles have three monoclinic crystal phases (m-zirconium dioxide) phase which is stable at room temperature, and the tetragonal (t-zirconium dioxide) phase present in the temperature range of 1100-2370°C and the cubic (c-zirconium dioxide) phase which is stable above 2370°C temperature [7]. Different approaches are utilized for the preparation of zirconium dioxide nanoparticles which includes the hydrothermal method, sol-gel method,

solvothermal method, thermal decomposition method aqueous precipitation method and pyrolysis of zirconium oxychloride salt organic precursors to successfully synthesize zirconium dioxide nanoparticles and these methods possess excellent properties to regulate the shape and size of nanoparticles which proved them more effective but sometimes often leads to the creation of mixed crystal phases. Besides this, these methodologies need high temperatures, are also costly, and produce chemical precursors which are harmful to the environment during the preparation of nanoparticles [6]. But nowadays green chemistry via biological approach got much attention from the researcher for the synthesis of metal nanoparticles and also the method are environmentally friendly to prepare nanoparticles which are the safest method [8]. So, the green

synthesis method is safe to prepare metal nanoparticles and also eco-friendly [9, 10]. Besides this using the chemical method for the preparation of nanoparticles generates various environmental poisonous chemicals which are dangerous for both environment and humans [11, 12]. Also, the chemical method is expensive so it's the need of today's science to develop other better alternative approach to synthesize nanoparticles and the green nanotechnology approach are one of the best alternative approaches to synthesize various metal nanoparticles in this method use various plant extract, other waste materials and fruits for the making of nanoparticles which efficiently decrease the use and production of poisonous chemicals [13]. In this review, we aim to focus on the biological preparation, characterization, and biological applications of zirconium dioxide nanoparticles.

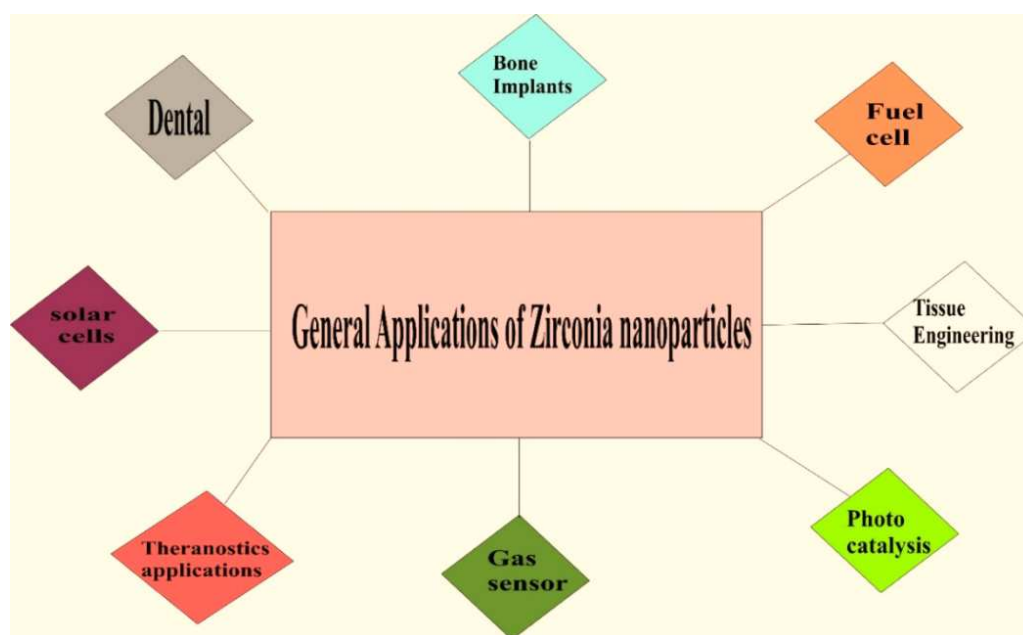


Figure 1. General applications of zirconium Nanoparticles.

2. Synthesis of Nanoparticles

Numerous approaches are utilized for the preparation of nanoparticles. These approaches consist of two classes which are top-down and bottom-up approaches. A top-down approach is a kind of destructive method in which smaller molecules are made from larger molecules and then the prepared smaller molecules are converted into appropriate nanoparticles, while the bottom approach is a kind of constructive approach which consists of gathering atomic size to prepare nano-sized particles [14]. The top-down approach consists of chemical etching, laser ablation, mechanical milling, electro-explosion, and sputtering. By using these various procedures the large size material is first altered into powder form and after that into specific nanoparticles. Both approaches have some limitations and advantages. There are many advantages of the top-down approach for instance synthesis of own size and the large quantity of NPs but exploiting this method has various

disadvantages which include high energy consumption, expansive, time-consuming, and also its leads to eco-toxicity [15, 16]. The bottom-up approach further consists of two methods such as biological and non-biological approaches. Furthermore, the non-biological approach further consists of atomic condensation, spinning, template support synthesis, laser pyrolysis, deposition of chemical vapors, and flame spraying but using these methods has also disadvantages which include time-consuming, expensive, and also use of toxic chemicals and biological approaches utilize different biotic resources which include a microorganism, plants, algae, and other biological molecules include gelatin, starch, egg albumin for the synthesis of various types of nanoparticles and these approaches are also called green approach [15, 17]. Utilizing this approach for the preparation of NPs is simple, reliable, ecofriendly, biocompatible, and simple. However, in this review, we only focus on the green synthesis of zirconium dioxide NPs, and their biological applications.

3. Green Synthesis of Zirconium Dioxide NPs (Biological Methods)

Using physical and chemical approaches (traditional approaches) has various disadvantages which include releasing a highly toxic chemical into the environment which is toxic to the ecosystem, time-consuming, expensive, and also requires high energy consumption. To control these issues green approaches are now applicable for the preparation of nanoparticles. As compared to the traditional approach the green-mediated approach has a lot of advantages which are biocompatible, ecofriendly, and also more interesting [18, 19]. In this method, various plants/ parts of plants are used for the preparation of nanoparticles also using fruits, fungi, bacteria, algae, and other biological molecules including egg albumin and starch which are acting as capping/ reducing/ and oxidizing agents [20, 21].

3.1. Green Synthesis Using Plant Extracts

In Nanobiotechnology using green approaches for the preparation of metal oxide nanomaterial is an emerging research area nowadays and the importance of this method over the chemical/physical method is that this approach is safe facile swift cost-effective and also can easily produce a large scale of NPs and also utilizing this approach no requirements of energy, pressure, increase temperature and toxic chemical [6, 22]. Utilizing plant material for the preparation of zirconium dioxide nanoparticles got much attention because of the simple, nontoxic, rapid environmentally safe, cost-effective, and easy one-step process to prepare NPs [22, 23]. The plants contain various combinations of biomolecules that help in the stability of ZrO_2 nanoparticles these biomolecules include tannins, sugar, steroid, enzymes, phenols, amino acids, flavonoids, and sugar which are mostly present in plants extracts and important for the medicinal purpose [24, 25]. Various plants are reported for the preparation of zirconium nanoparticles and mentioned in this review. Diverse parts of plants are used for the production of zirconium dioxide nanoparticles to prepare various morphology nanoparticles and for the stabilization of nanoparticles various water-soluble heterocyclic components are responsible and also different procedures are utilized for the characterization of prepared NPs. In a recent study, *Acalypha Indica* aqueous leaf extract is used for making zirconium dioxide NPs and the average size of the prepared NPs have observed 20-100nm [26]. Similarly, *Camellia oleifera* (*C. oleifera*) seed shells are used to prepare zirconium dioxide/biochar. The prepared materials have an excellent ability to absorb of fluoride in water [27]. *Aloe Vera* plant-based zirconia nanoparticles are prepared and further characterization is performed through different techniques including XRD, SEM, UV-Vis, FTIR, AFM, and also thermogravimetric and differential analysis are performed and the characterization study displayed that the synthesized NPs have a spherical shape and 50-100nm in size and have

good antibacterial and antifungal activity [22]. Similarly, *Nyctanthes arbor-tristis* flower extract-based zirconia nanoparticles are reported and due to the presence of water-soluble carbohydrates nano- sized zirconium dioxide nanoparticles are prepared and the prepared nanoparticles are characterized through various techniques including TG/DTA, UV, EDX, AFM, and SEM. Further study confirmed that the prepared nanoparticles have excellent antimicrobial performance and showed better activity against *E. coli* as compared with *S. aureus* when the same concentration of zirconium dioxide nanoparticles are tested against these bacterial strains [28]. Furthermore in another research *Euclea natalensis* (also known as Natal gwarri) plant extract is used for the preparation of zirconia nanoparticles. Further adsorptive properties are tested against tetracycline antibiotics and the prepared nanoparticles are characterized through TEM. FTIR and XRD techniques revealed that synthesized material has a minimum crystallite size of 5.25nm [29]. Similarly, rubber latex is utilized for the making of zirconium NPs and the prepared nanoparticles have a tetragonal structure [30]. Similarly, *Wrightia tinctoria* leaf extract is exploited for the preparation of zirconium dioxide nanoparticles to determine the anti-bacterial and photocatalyst activity of the nanoparticles. Furthermore, characterization of the prepared nanoparticles is performed through various techniques which include FTIR, UV-Vs, SEM, XRD, EDAX, and DLS, and further, the XRD confirms the tetragonal crystal structure of the nanoparticles and average size of 9.15nm [31]. *Curcuma longa* tuber-based zirconia nanoparticles are prepared and the water-soluble organic is responsible for the preparation of NPs which convert ZrF_6^{2-} ions to ZrNP and the average size of the nanoparticles are confirmed 41-45nm [32]. Similarly, *Ficus benghalensis* (F.B.) leaf extract is utilized for the preparation of zirconia nanoparticles and the prepared nanoparticles are characterized through UV-Vis, TEM, XRD, DRS, FT-Raman, and HR-TEM and further, the XRD analysis confirms the syntheses and monoclinic and tetragonal structure of the nanoparticles. Furthermore, TEM revealed spherical morphology and 15 nm size of the nanoparticles and the prepared nanoparticles have excellent photocatalytic activity [23]. *Laurus nobilis* (bay leaf) aqueous leaf extract is reported for the making of zirconia NPs and the prepared nanoparticles are characterized through various analytical techniques including UV-Vs, XRD, FTIR, DLS, and SEM and these characterization techniques confirmed the diameter from 20 to 100 nm and also the development of nanoparticles and also results showed that synthesized nanoparticles are an excellent antimicrobial agent and will be useful for medical industry [33]. Similarly, *Justicia adhatoda* extract is used to synthesize CeO_2/ZrO_2 core metal oxide NPs and the preparatory method is carried out at room temperature to get core metal oxide NPs. Further, the growth, under nucleation, aggregation process, morphological properties, and the crystalline surface are examined through TEM, XRD and SEM studies and the prepared CeO_2/ZrO_2 core metal oxides indicated nano stick agglomerated structure having a size of

20-45nm and the results displayed that the prepared material will be a useful biomedical agent in future [34]. In another research *Capsicum annum*, *Allium cepa*, and *Lycopersicon esculentum* extracts are used for the preparation of zirconium dioxide nanoparticles and results displayed that all the nanoparticles have excellent properties and all are crystal shape Baddeleyite and the nanoparticles synthesized by *C. annum* through method one and method two and the average size of nanoparticles are recorded 100.25nm. 86.66 nm and the synthesized nanoparticles have excellent antibacterial and antifungal activities [5]. Similarly, Helianthus annuus (sunflower) seeds are used to prepare zirconia nanoparticles and successful y monoclinic zirconia nanoparticles are synthesized further the x-ray diffractometry showed that the synthesized zirconia are crystallite having a size of 40.59nm and prepared nanoparticles have excellent antimicrobial activity [35]. Lagerstroemia speciosa Leaves are utilized for

the creation of zirconia nanoparticles and further, the prepared nanoparticles are characterized by various analytical tools which include TEM, FTIR, XRD, SEM, EDX, and TGA analysis and further photocatalytic activity of zirconium oxide nanoparticles are studied against azo dye which showed that the synthesized nanoparticles degrade 94.58% azo dye [36]. Similarly, zirconium nanoparticles powder are synthesized from Azadirachta indica and *aloe Vera* plant extract, and the antibacterial activity against oral pathogens and cytotoxic effect is determined through shrimp lethal assay which showed that the prepared nanoparticles can be used against oral pathogens in a small amount [37] Different plants which facilitate the synthesis of zirconia dioxide nanoparticles are mentioned in Table 1. Several parts of the plant which includes the tuber, leaves, fruit, and flower are utilized for the making of ZrO₂ NPs in diverse shapes and size via biological approaches.

Table 1. Synthesis of zirconia nanoparticles from various plant species.

SR.No	Plant Taxa	Part used	Shape	Size (nm)	Characterization	Phyto-constituents Present in plant	References
1	<i>Ficus benghalensis</i>	Leaves	Spherical	15 nm	UV-VIS, DRS, XRD, FT-IR	carboxyl groups, amines	[23]
2	<i>Capsicum annum</i>	Fruit	Baddeleyite	13.06-22.02 nm	AFM, UV-VIS, XRD, FT-IR	-	[5]
3	<i>Allium cepa</i>	Fruit	Baddeleyite	13.03-21.97 nm	AFM, UV-VIS, XRD, FT-IR	-	[22]
4	<i>Lycopersicon esculentum</i>	Fruit	Baddeleyite	20.48-21.37 nm	AFM, UV-VIS, XRD, FT-IR	-	[6]
5	<i>Aloe vera</i>	Leaves	Spherical	50-100 nm	XRD, SEM, EDX, FTIR, UV-VIS	Carboxylic acid And phenolic groups	[22]
6	<i>Eucalyptus globulus</i>	Leaves	Spherical	9-11 nm	RD, FTIR, TEM, SAED, EDX	Polyphenols, aliphatic amines, alkanes,	[6]
7	<i>Nyctanthes arbor-tristis</i>	Flower	-	-	TG/DTA, XRD, SEM WITH EDX, AFM AND UV	-	[28]
8	<i>Lemon juice</i>	Fruit	Quasi-spherical	21 nm	EDS, AAS, XRD, UV-VIS, PL SPECTROSCOPY	carboxylic acid, ester	[38]
9	<i>Lagerstroemia speciosa</i>	Leaves	Tetragonal	56.8 nm	FT-IR, TEM, XRD, EDX, SEM	carboxylic group, amino group	[36]
10	<i>Sargassum wightii</i>	-	Spherical	4.8 nm	XRD, FTIR, HR-TEM, UV-VIS, PL SPECTROSCOPY	carboxylic acid group, alcoholic groups	[39]
11	<i>Acalypha indica</i>	Leaves	Cubic	20-100 nm	FTIR, XRD, SEM, EDX	-	[26]
12	<i>Azadirachta indica</i>	Leaves	-	-	UV-VIS SPECTROSCOPY, XRD	-	[40]
13	<i>Curcuma longa</i>	Tuber	Chain	41-45 nm	TEM, EDX, FTIR	-	[32]
14	<i>Camellia oleifera</i>	seed	-	-	SEM, EDS, XPS, FTIR	-	[27]
15	<i>Euclea natalensis</i>	-	-	5.25 nm	XRD, FTIR, TEM	-	[29]
16	<i>Wrightia tinctoria</i>	leaf	Tetragonal	9.15 nm	XRD, FTIR, TEM	-	[31]
17	<i>Laurus nobilis</i>	leaves	Spherical	20-100nm	XRD, SEM TEM	-	
18	<i>Justicia adhatoda</i>	-	-	20-45 nm	XRD, SEM TEM	alkaloids, terpenoids, flavonoids	[34]
19	<i>Helianthus annuus</i>	seed	Monoclinic	40.59 nm	UV-VIS, SEM, TEM	-	[35]
20	<i>Tinospora cordifolia</i>	leaves	-	73nm	FESEM, EDX, FTIR, XRD	alkaloids, flavonoids, glycosides, tannins	[35]
21	<i>Averrhoa bilimbi</i>	fruit	-	10-50 nm	MS, XRD, TEM, SEM	-	[41]
22	<i>Terminalia chebula</i>	seed	-	15.52	SEM, EDAX, FTIR, XRD	alkaloids, flavonoids, phenols, carbohydrates, glycosides, terpenoid, saponin	[42]

3.2. Fungal Mediated Synthesis of Zirconium Dioxide NANOPARTICLES

Microorganisms are used in green nanotechnology to synthesize nanoparticles (NPS). Many microorganisms are known to accumulate inorganic compounds inside or outside

the cell to synthesize nanoparticles. Whereas many microbial species can produce metal NPs and microbial NP production is a green chemistry strategy that fills the gap between nanotechnology and microbial biotechnology and many studies reported that bacteria, actinomycetes, fungi, yeasts, and viruses can produce Au, Ag, gold alloy, selenium, tellurium, platinum, palladium, silica, titania, zirconia,

quantum dots (QDs), magnetite, and uraninite NPs [43]. Mycosynthesis of metal NPs, also known as myco nanotechnology (MNT), is the use of fungi in NT to produce nanoparticles. The capacity of filamentous fungi to grow on commonly available and affordable substrates and have the capability to generate a wide variety of commercially interesting metabolites has sparked significant interest in using them as biotechnology manufacturing microorganisms [43]. We will only explain the synthesis of zirconium dioxide nanoparticles and their medical applications in this section. For the first time, zirconium NPs are prepared using *Penicillium* species as a dependable and environmentally friendly procedure. Several analytical tools are used to analyze the prepared nanoparticles which include DLS, EDX, FTIR, AFM and SEM. Three *Penicillium* species were found to be capable of extracellularly synthesizing zirconium NPs with spherical morphology less than 100 nm. Furthermore, study showed that the prepared nanoparticles have excellent antibacterial activity against gram-negative bacteria [44]. *Fusarium solani*, a Phyto-pathogenic fungus, are utilized for making of zirconium oxide (ZrO₂) nanoparticles which acts as a reducing and stabilizing agent. Further morphological and structural properties of zirconium dioxide nano-powder are studied. The XRD pattern demonstrated a peak at the 2θ = 30° (111) plan, indicating a tetragonal structure. HRTEM are used to examine the morphology of the calcined nanoparticles, which confirmed that they were spherical [45]. The fungus *Fusarium oxysporum* can be challenged with aqueous ZrF₆ 22 anions to produce zirconia nanoparticles; extracellular protein-mediated hydrolysis of the anionic complexes results in the facile room-temperature synthesis of nanocrystalline zirconia. Intracellularly hydrolysis of metal anions by cationic proteins with molecular weights ranging from 24 to 28 kDa, which are closely related to silicatein in nature, is seen to be essential for the formation of zirconia nanoparticles, opening up the exciting possibility of large-scale biological synthesis of technologically important oxide materials [46]. The total protein content activity was used to evaluate the ability for zirconium nanoparticle (Zr-NP) biosynthesis in various stages of growth of *Penicillium notatum*, *P. purpurogenum*, and *P. aculeatum*. Fungal secreted protein concentrations were greater in all three species during the deceleration phase. Different pH values and ZrCl₄ concentrations were studied and evaluated to improve

biosynthesis requirements in terms of Zr-NP size [47].

3.3. Bacterial Mediated Synthesis of Zirconium Nanoparticles

Bacteria have significant capabilities to reduce heavy metal ions and could be used to produce nanoparticles. Metal, metal oxide, and other novel nanoparticles were synthesized using various bacterial species [48]. *Pseudomonas aeruginosa* bacteria are utilized to prepare zirconia NPs using green technology for adsorption-driven bioremediation of tetracycline from wastewater. Furthermore, different characterization techniques are utilized for the characterization of prepared nanoparticles which includes XRD, FETEM, FTIR, XRD, DLS, energy dispersive X-ray, and point of zero charge analysis are used to characterize synthesized nano zirconia. Further study revealed that the synthesized particles have a 15nm average size and monoclinic, tetragonal structure with a crystallite size of 6.41nm and also contain various functional groups which include O–Zr–OH, Zr–O–Zr, and Zr–O bonds, oxygen and elemental [49]. Extremophilic *Acinetobacter* sp. KCSII, are utilized for the preparation of crystalline ZrO₂ nanoparticles through a single pot at room temperature and is characterized by utilizing several procedures to study their structural, optical, and crystalline properties. The ZrO₂ nanoparticles have been reported to have an average size of 44.7 nm. Furthermore, the prepared zirconium dioxide nanoparticles are tested against mouse fibroblast cells (L929) and no cytotoxicity of the prepared nanoparticles is studied which indicated that the prepared nanoparticles are safe and efficient for environmental and biomedical applications [50]. *Pestalotiopsis Versicolor* is a highly damaging fungus that causes bayberry twig blight disease. For the first time, zirconium oxide nanoparticles' biological activity is confirmed against *P. Versicolor*. The strain used for ZrO NPS *Enterobacter* sp. strain RNT10. The presence of ZrO NPs in the reaction mixture are confirmed using UV–vis spectroscopy. Furthermore, FTIR, XRD, SEM, and TEM analyses revealed the presence of capping proteins as well as the crystalline nature of spherical-shaped ZrONPs with particle sizes ranging from 33 to 75 nm [51]. Various fungal and bacterial mediated zirconium nanoparticle synthesis are shown in Table 2.

Table 1. Synthesis of zirconia nanoparticles from various fungal and bacterial species.

SR. No	Fungi Taxa	Shape	Size (nm)	Characterization	Constituents present	References
1	<i>Penicillium</i> species	spherical	100 nm	SEM, AFM, FTIR, EDX	N/A	[44]
2	<i>Fusarium solani</i>	spherical	30-40 nm	FT-IR, XRD, HRTEM	aliphatic amine, hydroxyl groups	[45]
3	<i>Fusarium oxysporum</i>	quasi-spherical	3 -11 nm	SAED, XRD, FTIR	N/A	[46]
4	<i>Penicillium notatum</i> , <i>P. purpurogenum</i> and <i>P. aculeatum</i>	spherical	-	SEM, EDX, DLS, FTIR	NADH, NADH-dependent nitrate reductase enzymes, primary amides	[47]
Sr.No	Bacterial species	Shape	Size (nm)	Characterization	Constituents present	References
1	<i>Enterobacter</i> sp.	spherical	33 -75	FTIR, XRD, SEM and TEM	hydroxyl (O-H) group, alkene group	[51]
2	<i>Acinetobacter</i> sp	-	44 ± 7	SAED, HRTEM, XRD, FM	N/A	[50]
3	<i>Pseudomonas aeruginosa</i>	spherical grains	6.41	FTIR, XRD, DLS	N/A	[49]

3.4. Algal-Mediated Synthesis of Zirconia Nanoparticles

Algae are progressively being used in green synthesis because they are a high source of secondary metabolites, proteins, peptides, and pigments that can be used as nano-bio factories. Furthermore, they have a rapid growth rate, are easy to harvest, and can be scaled up at a low cost, making them ideal contenders for the biological preparation of nanoparticles. Algae are the most primitive organisms on earth, dwelling in diverse ecosystems and dominating photosynthetic organisms. Algae can hyper-accumulate metals and convert them into nanoparticles, which makes them the perfect choice for nanoparticle preparation. Many metallic and metal oxide nanoparticles (NPs) are created from algae, including blue-green algae (Cyanophyceae), brown algae (Phaeophyceae), and green algae (Chlorophyceae), and red algae (Rhodophyceae) [52]. A simple and environmentally friendly combustion technique has been developed for the creation of zirconia (ZrO_2) nanoparticles utilizing the marine brown alga (seaweed), *Sargassum wightii* (*S. wightii*). Furthermore, XRD, FTIR, HR-TEM, UV-vis, and PL spectroscopy are utilized to evaluate the structural, optical, and photoluminescence properties of the prepared ZrO_2 nanoparticles. Because of their greater surface area and nano-size, the synthesized zirconia NPs have a significant antibacterial effect against *B. subtilis*, *E. coli*, and *S. typhi* [39].

4. Biomedical Application

4.1. Antibacterial Activity of Zirconia NPs

As bacterial resistance is increasing nowadays is most challenging to produce novel antibiotic agents to treat bacterial diseases and among the novel antibiotic agents, metal nanoparticles showed improved antibacterial performance against bacteria. As bacterial resistance are increasing in a short period so developing novel antibiotic are challenging and released to the market. As nanoparticles have improved antibacterial performance a lot of nanoparticles are developing against bacteria because the nanoparticles target various biomolecules of the resistant strain [53]. Similarly, *Aloe Vera* plant-based zirconia nanoparticles are synthesized which have a homogenous spherical distribution and an average size of 50-100nm and improved antibacterial ability against *E. coli* and *S. aureus* and also have excellent performance against *Candida albicans* and *Aspergillus niger* [22]. Also, bacterial and fungal activities of zirconia and zirconia mixed ligand are reported and the results revealed that zirconia has excellent activity against *E. coli* and also the Zr(IV) complexes showed excellent performance against both gram-positive *S. aureus* and gram-negative *E. coli* and also displayed excellent performance against *A. niger* fungus [54]. Similarly, zirconia nanoparticles are synthesized from marine brown alga seaweed called *sargassum wightii* and further bacterial activity of the prepared nanoparticles is determined against

both gram-positive and gram-negative strains of bacteria through well diffusion assay and the prepared nanoparticles displayed excellent activity against *E. coli*, *S. typhi*, and *Bacillus subtilis* because of their large surface area by their size [39]. Zirconium oxide nanopowder has improved antibacterial performance so, undoped and dysprosium – doped zirconium dioxide nanopowder is synthesized through the co-precipitation method by utilizing dysprosium (III) nitrate pentahydrate and zirconyl nitrate as starting material and further the antibacterial activity of the prepared doped oxide is determined against *B. subtilis* and *K. pneumonia* which showed improved bactericidal efficiency as compared with undoped oxide [55]. Similarly, zirconium nanoparticles powder are synthesized from *Azadirachta indica* and *aloe Vera* plant extract, and the antibacterial activity against oral pathogens and cytotoxic effect is determined through shrimp lethal assay which showed that the prepared nanoparticles can be used against oral pathogens in small amounts and in small concentrations, *S. aureus* showed an 8mm zone of inhibition when the concentration increased *S. mutans* showed 11mm zone of inhibition [37]. Similarly *Wrightia tinctoria* leaf extract are used for the preparation of ZrO_2 nanoparticles and further photo-catalyst and antibacterial activity of the prepared nanoparticles are evaluated and the photocatalytic degradation is performed under sunlight irradiation to degrade organic dye reactive yellow (RY 160) and the results showed that prepared nanoparticles can degrade 94% organic dye. Furthermore, the antibacterial performance of the prepared nanoparticles is determined against gram-positive and gram-negative bacteria which showed that the prepared nanoparticles have good antibacterial activity [31]. Furthermore, zirconium dioxide nanoparticles are prepared through the hydrothermal method which is further characterized by various analytical techniques including SEM, XRD, UV-s, and FTIR. These analytical techniques confirmed the presence and morphology of the prepared nanoparticle. Further antibacterial activity of the prepared nanoparticles is determined against *Staphylococcus aureus* with different concentrations which confirmed that increasing the concentration of the prepared nanoparticles increases antibacterial performance and zone of inhibition [56]. Surface-modified zirconium dioxide nanoparticles are synthesized through the solvothermal method. In this method, the surface of zirconium dioxide is functionalized with glutamic acid which is an amino acid containing COO^- and NH_4^+ ions to increase its antimicrobial properties. Furthermore, the prepared GA- ZrO_2 nanoparticles are tested against four oral bacterial strains including *Rothia mucilaginosa*, *Rothia dentocariosa*, *Streptococcus mitis*, and *Streptococcus mutans* to determine their antibacterial activities. Further, the results confirmed that prepared GA- ZrO_2 showed excellent antimicrobial activities [57].

4.2. Antifungal Activity of Zirconium NPs

Fungi are creating destruction of crop productivity and

also human pathogenic fungi also cause problems in human evolution due to their presence in any habitat. Due to encrypting gene rearrangement and easy adoption in any environment showing resistance to traditional fungicides so to minimize this issue an effective and immediate strategy is needed to overcome this problem [58]. Different nanoparticles are developed against fungus which showed the best response against fungi. Recently Zirconium dioxide nanoparticles are prepared against *Rhizoctonia solani* to develop root rot resistance in cucumber. Furthermore, the results displayed 86.6% growth inhibition of *Rhizoctonia solani* at 100 µg/L of zirconium dioxide nanoparticles which showed that the prepared nanoparticles have excellent ability against fungus. Further at field conditions, the prepared nanoparticles showed 52-56% inhibition in comparison to the greenhouse effect (34-46%) of root rot disease. Besides this use of zirconium nanoparticles, carboxin+ thiram increases the growth of cucumber [59]. Similarly, Zirconium dioxide nanoparticles are synthesized against *Pestalotiopsis versicolor* fungus which causes twig blight disease in bayberry and the strain used for the preparation of zirconium oxide nanoparticles are *Enterobacter* species strain RNT10 and the prepared nanoparticles are then characterized through different analytical techniques which include SEM, TEM, FTIR and XRD. Further, the SEM and TEM analysis confirmed the spherical shape of the prepared nanoparticles which have an average size of 33-75 nm. Furthermore, the prepared nanoparticles showed an excellent antifungal zone of inhibition (25.18 ± 1.52 mm) at 20 µg mL⁻¹ concentration when tested against *P. versicolor* strain XJ27 [51]. Zirconium oxide-Ag₂O nanoparticles- synthesized through the sol-gel method showed excellent antifungal activities against various fungus species. Furthermore, the prepared nanoparticles are analyzed through various analytical techniques which include DLS, UV-vis, Raman, and scanning electron microscope, and then the prepared nanoparticles are later tested against different fungal species including *Candida tropicalis*, *Candida albicans*, *Candida dubliniensis*, and *Candida glabrata* through disc diffusion and microdilution method and the results showed that prepared nanoparticles are more effective against *Candida* species [60].

4.3. Anticancer Activity of Zirconium NPs

Cancer is one of the most death-causing diseases which are mostly caused due to mutation in proto-oncogenes expression patterns, in those genes which are involved in DNA repairs and tumor suppresser genes [61]. The disease-causing a high number of deaths worldwide and according to the National cancer institute, fourteen million new cancer cases are reported in 2012, and also 8.2 million cancer-causing deaths are reported [61]. Due to their high rates of death, it's a strong need to develop a novel efficient strategy for treatment and efficient diagnosis of cancer. In the last decades, nanotechnology and nanoscience have developed hope in researchers because of their efficient role in cancer treatments [61]. So to overcome these problems recently zirconium nanoparticles are synthesized from lemon and

lemon peel with zirconium salt further the prepared nanoparticles are tested against MCF-7 cancer cell lines and also tested its bioactivity against free radicals and the prepared NPs + Peel showed the highest percentage effect 95.16 anticancer activity against MCF-7 cell lines and lowest effect 18.42 and this proved that the prepared nanoparticles have excellent anti-cancer properties [62]. Similarly, *Eucalyptus globulus* (*E. globulus*) leaf extract-based zirconium nanoparticles are reported and the prepared nanoparticles have a small size of 9-11nm having a spherical shape. Furthermore, the biological activity cytotoxicity against human colon carcinoma (HCT-116), and human lung carcinoma (A- 549) cell lines of the prepared nanoparticles are studied also the antioxidant activity is determined and the results displayed that prepared zirconium dioxide nanoparticles have effective anticancer and antioxidant activity [6]. Furthermore, zirconium dioxide nanoparticles coated with platelet membrane (PLTm) named PLT@ZrO₂ are synthesized and the prepared PLTm nano vesicles camouflage zirconium dioxide nanoparticles have an efficient ability to target tumor sites and are easily able to clear by macrophages. Also, the prepared PLY@ zirconium dioxide nanoparticles have efficient invasion and inhibiting of metastasis of Hela cells both in vitro and in vivo. Furthermore in vivo confirmed that the prepared materials showed efficient inhibition of tumor growth in xenograft mice and also inhibited liver metastasis of Hela cells and lungs which proved that prepared material will be suitable as an anticancer agent in future research [63].

4.4. Zirconium Nanoparticles in Tissue Engineering Applications

Tissue engineering is a much advance and fascinating field of research and but preparing suitable tissue engineering scaffolds is of much challenging [64]. Recently zirconia, nanoscale silicon dioxide, and chitosan are combined and prepared bio composite scaffold through freeze-drying technique, and further prepared materials are characterized through FTIR, SEM, and XRD. Furthermore, the study confirmed that prepared materials are efficient for bone tissue engineering applications because due to the existence of zirconia in the scaffold decreased swelling and increased biodegradation [64]. Similarly, zirconium dioxide nanoparticles are prepared through the vapor phase hydrolysis process which is further characterized by XRD, AFM, and Vickers hardness test method to determine crystalline structure and hardness. Furthermore, hemolysis assay and in vitro cytotoxicity evolution confirmed that the preparation material is biocompatible. Further, the prepared zirconium dioxide nanoparticles at 500°C under 6MPa are pressed into flakes and sintered then at 1400°C the prepared flakes showed an optimal combination of hardness (534.58 gf·mm⁻²), roughness (0.07 µm) and density (4.41 g·cm⁻³). Furthermore experimental results confirmed that the prepared materials are efficient for biomedical applications, especially for tissue engineering and bone [65].

4.5. Other Applications of Zirconium Nanoparticles

As zirconium dioxide nanoparticles have numerous applications in different fields and different methods are utilized for the synthesis of Zirconium dioxide nanoparticles but the biological approach is much safe and benefits over other chemical approaches and zirconium nanoparticles have excellent biological activity against different microorganisms and also possess excellent photocatalytic activity due to which it has a various application which includes the gas sensor, fuel cell bone implants, and similarly, zirconium dioxide nanoparticles are synthesized from *Ficus benghalensis* leaves extract and the prepared nanoparticles have excellent photocatalytic activity and showed improved photodegradation of methylene blue and methyl orange within 240 minute [23]. Dawar et al. have reported zirconium dioxide nanoparticles from lemon juice and the prepared nanoparticles possess excellent electrolyte material in solid oxide fuel cells [38]. Also, spherical mesoporous zirconia nanoparticles are prepared through the sol-gel method which is biocompatible cell-permeable, and degradable and will be exploited for theranostics applications [66]. Nanoscale zirconium oxide and Zirconium oxide (ZrO_2) nano powdered are synthesized and the prepared nanoscale ZrO_2 has excellent mechanical stability and biocompatibility and will be suitable for use in tissue engineering and dentistry [67]. Zirconium dioxide nanoparticles-rGO hybrid is prepared through the hydrothermal method and the prepared materials have excellent applications as supercapacitors, sensors, biosensors, and fuel cells [68]. Graphene nanosheet decorated zirconia nanoparticles are reported and prepared through an electrochemical approach the prepared graphene nanosheet decorated zirconia nanoparticles are efficient for capturing organophosphate pesticides [69]. Similarly, oxide bio probes based on sub-5 nm amine-functionalized tetragonal $\text{ZrO}_2\text{-Ln}^{3+}$ nanoparticles are prepared through the solvothermal method and will be exploited for bio imaging [70]. As zirconia nanoparticles have a role in additive concrete structure Similarly zirconia nanoparticles are synthesized which are characterized through XRD, UV-Vs, and TEM, and the average particle size of 20 nm and will be exploited as additives concrete [71].

5. Conclusion

This review describes the biological preparation of Zirconium nanoparticles and their numerous application in biomedical science. Therefore special attention is required of the scientific community because this method is a more simple, nontoxic environmentally friendly, and commercially viable approach for the preparation of Zirconium oxide NPs using green chemistry bottom to top approach and using plant extract materials potentially effective over chemical method. Therefore in the future era, more works will be exploited to use this green approach for the preparation of metal oxide NPs because this method is safe and reduce the

cost of chemicals. Therefore, further work is needed to use plant parts to develop zirconium oxide nanoparticles and explore their biomedical applications.

Conflict of Interest

The authors declare that they have no competing interests.

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