Introduction

1.0- Nanotechnology

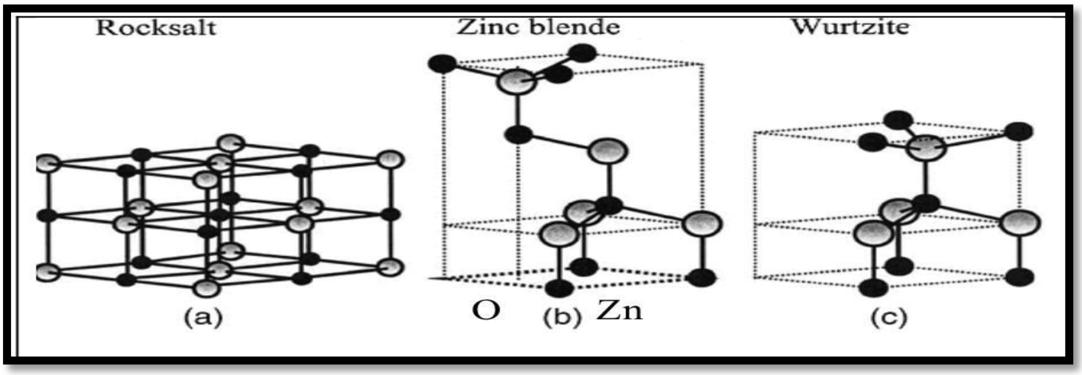
Nanotechnology is an emerging technology, which can lead to a new revolution in every field of science [1]. This technology is used with association to optics, electronics, and biomedical and materials sciences. Research in this field has gained momentum in the recent years by providing innovative solutions in different scientific disciplines. Nanotechnology deals with nanoparticles that are atomic or molecular aggregates characterized by size less than 100 nm. These are actually modified form of basic elements derived by altering their atomic as well as molecular prop- erties of elements [2,3]. Nanoparticles gained considerable attraction because of their unusual and fascinating proper- ties, with various applications, over their bulk counterparts. Recently, biomedical nanomaterials have received more concerns because of their prominent biological character- istics and biomedical applications. With the development of nanomaterials, metal oxide nanoparticles show promising and far-ranging prospect for biomedical field, especially for antibacteria, anticancer drug/gene delivery, cell imaging, biosensing, and so on [4].

2.0- Zinc oxide nanoparticles (ZnO NPs)

as one of the most important metal oxide nanoparticles, are popularly employed in various fields due to their peculiar physical and chemical properties [5, 6]. ZnO NPs are firstly applied in the rubber industry as they can provide wearproof of the rubber composite, improve performance of high polymer in their toughness and intensity and antiaging, and other functions [7, 8]. Because of the strong UV absorption properties of ZnO, they are increasingly used in personal care products, such as cosmetics and sunscreen [9]. In addition, ZnO NPs have superior antibacterial, antimicrobial, and excellent UV- blocking properties. Therefore, in the textile industry, the finished fabrics by adding ZnO NPs exhibited the attractive functions of ultraviolet and visible light resistance, anti- bacteria, and deodorant [10]. Apart from the applications mentioned above, zinc oxide can also be used in other branches of industry, including concrete production, pho- tocatalysis, electronics, electrotechnology industries, and so on [7, 11]. It is generally known that zinc as an essential trace el- ement extensively exists in all body tissues, including the brain, muscle, bone, skin, and so on. As the main component of various enzyme systems, zinc takes part in body's metabolism and plays crucial roles in proteins and nucleic acid synthesis, hematopoiesis, and neurogenesis [5–8]. Nano-ZnO, with small particle size, makes zinc more easily to be absorbed by the body. Thus, nano-ZnO is commonly used as a food additive. Moreover, ZnO is graded as a "GRAS" (generally recognized as safe) substance by the US Food and Drug Administration (FDA) [12]. With these properties, ZnO NPs have received more attention in bio medical applications. Compared with other metal oxide NPs, ZnO NPs with the comparatively inexpensive and relatively less toxic property exhibit excellent biomedical applications, such as anticancer, drug delivery, antibacterial, and diabetes treatment; anti-inflammation; wound healing; and bio- imaging .Herein, in this review, we will summarize the methods of synthesis and recent exciting progress on the use of ZnO NPs in the biomedical fields. [4,13–15].

3.0- Basic Crystal Structures of ZnO

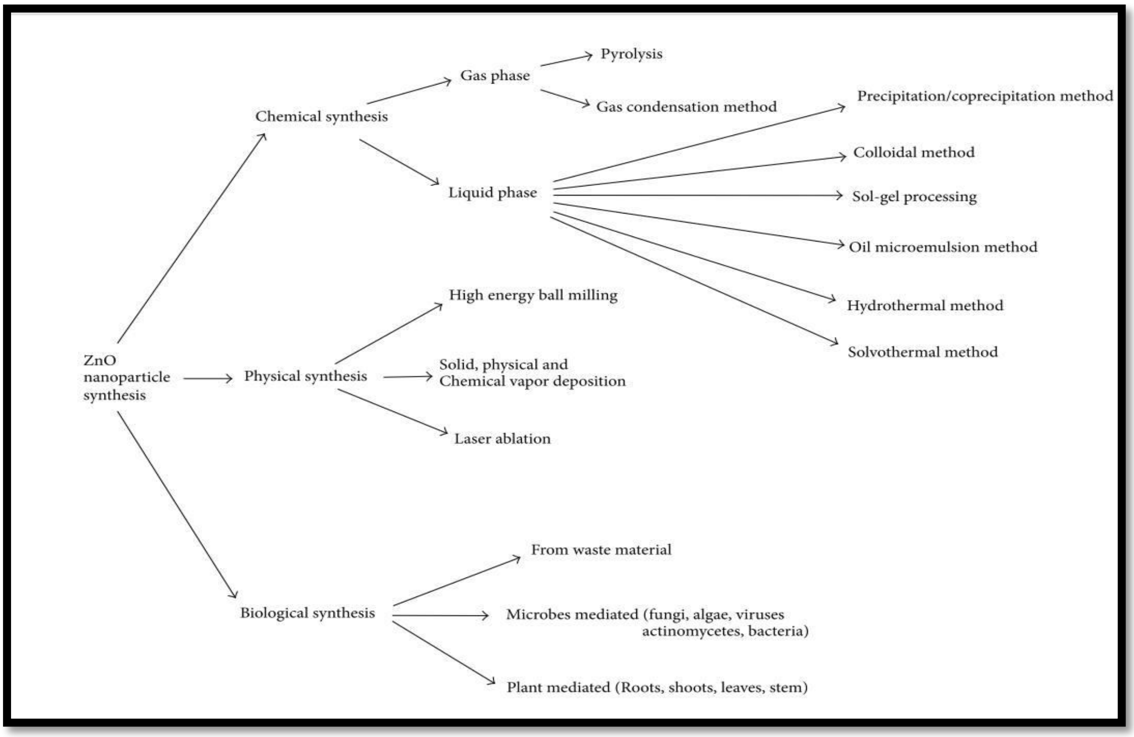
Zinc oxide crystallizes in three forms i.e. hexagonal wurtzite, cubic zincblende, and cubic rock salt. The wurtzite structure is most stable at ambient conditions and thus most common. The zincblende form can be stabilized by growing ZnO on substrates with cubic lattice structure. In both cases, the zinc and oxide centers are tetrahedral. The rock salt (NaCl-type) structure is rarely observed and it is only observed at relatively high pressures of about 10 Gpa. Despite of these three basic forms zinc oxide can be induced to form a very large variety of crystalline shapes using specialized growth. [15]



Figure(1) Stick and ball representation of ZnO crystal structures: (a) cubic rock salt, (b) cubic zinc blend, and (c) hexagonal wurtzite. [16]

4.0- Synthesis of ZnO NPs

The biological activity of nanoparticles depends on factors including surface chemistry, size distribution, particle morphology, and particle reactivity in solution. Therefore, the development of nanoparticles with controlled structures that are uniform in size, morphology, and functionality is essential for various biomedical applications. The ZnO NPs occurring in a very rich variety of size and shape will provide a wide range of properties. The methods for stable ZnO NPs preparation have been widely developed in recent years, which mainly include the chemical pre- cipitation method, sol-gel method, solid-state pyrolytic method, solution-free mechanochemical method, and bio- synthesis method.[17]



Figure(2) Major synthetic techniques used for ZnO nanoparticles synthesis. [18]

4.1- Chemical Precipitation:

The most popular method for ZnO NPs preparation is chemical precipitation, which usually involves two reaction reagents: a highly purified zinc forerunner such as zinc acetate (Zn (CH3COO)2·2H2O), zinc nitrate (Zn(NO3)2), or zinc sul- fate (ZnSO4) and a solution of precipitator such as sodium hydroxide (NaOH) or ammonium hydroxide (NH3·H2O). [19]

Advantages of Chemical Synthesis: Chemical synthesis can be performed by using a range of precursors and different conditions like temperature, time, concentration of reactants, and so forth. Variation of these parameters leads to morphological differences in size and geometries of resulting nanoparticles.

Disadvantages of Chemical Synthesis of Nanoparticle: The chemical synthesis methods of ZnO NPs like chemi- cal precipitation, hydrothermal method, pyrolysis, chemical vapour deposition, and so forth result in the presence of some toxic chemicals adsorbed on the surface that may have adverse effects in medical applications. There are some reactions in these chemical procedures which require high temperature and high pressure for their initiation while some reactions require inert atmosphere protection or inert conditions. Some chemical techniques also involve utilization of certain toxic matters such as H2S, toxic template, and metallic precursors . The chemicals used for synthesis of nanoparticles and for their stabilization are toxic and lead to nonecofriendly by products [20].

4.2- Biological synthesis:

The biological synthesis of ZnO NPs using fungi is a promising approach due to their high tolerance to higher metal concentration, high binding capacity and their ability in metal bioaccumulation over bacteria. Moreover, the fungi exhibited the ability to secrete a large number of extracellular redox proteins and enzymes. As such, this contributed to the reduction of the metal ions into NPs in larger amounts, which is suitable for the large-scale production. Synthesis and modification of bio-derived antibacterial Ag ,and ZnO nanoparticles by plants.[21]

The biosynthesis of metal and metal oxide NPs by plants, fungi, and bacteria could be a promising way to obtain biocompatible NPs that have desirable antibacterial activities. However, the uniformity of shape, size, and size distribution of NPs are crucial to producing significant antibacterial results, particularly in physiological conditions such as infected wounds or septicemia. In this review, we discuss recent progress and challenges in the use of novel approaches for the biosynthesis of Ag and ZnO nanoparticles that have antibacterial activities.

Biological method has developed immense interest due to its economic views, eco-friendliness, feasibility, and a broad range of applications in several fields such as catalysis, medicine, and agriculture.[21]

4.3- Green Synthesis :

Green synthesis procedures involve the plant based synthesis of nanoparticles. Green synthesis techniques make use of somewhat pollutant-free chemicals for synthesis of nanos- tructures. It embraces the use of ecofriendly and safe solvents such as water, natural extracts. So biological approaches using microorganisms and plants or plant extracts for synthesis of metal nanoparticles have been suggested as safe alternatives to chemical methods. In biogenic synthesis of nanoparticles, several biological systems including bacteria, fungi, and yeast have been used safely. But synthesis of nanoparticles by using microor- ganisms is somewhat difficult because it involves elaborate process of maintaining cell cultures, intracellular synthesis, and multiple purification steps.[22]

Advantages of green synthesis of nanoparticles: Inpresent times “green” method in the synthesis of nanoparticles has greatly become a topic of interest because the conventional chemical methods are expensive and require the use of chemical compounds/organic solvents as reducing agents which are toxic as well [23].

Green chemistry reduces pollution risk at source level and it is enhanced to prevent waste rather than treat or clean up waste after it is formed. The principle focuses on choice of reagents which are ecofriendly. Although physical and chemical methods are quick and easier for nanoparticles synthesis the biogenic technique is better and ecofriendly [24, 25].

By Using Leaf Extract of Coriandrum sativum. ZnO NPs can be synthesized by using the leaves extract of plant Corian- drum sativum.

Toxicological Implications of Green Synthesis of ZnO: Instability of biologically synthesized nanoparticles is worth consideration. Physical instability of nanoparticles may alter their arrangement/confirmations due to different conditions like temperature pressure, light, medium, pH, and so on, which may lead to the creation of the different unwanted chemical moieties. Moreover, potential hazards of these chemical metabolites are very poorly investigated[25].

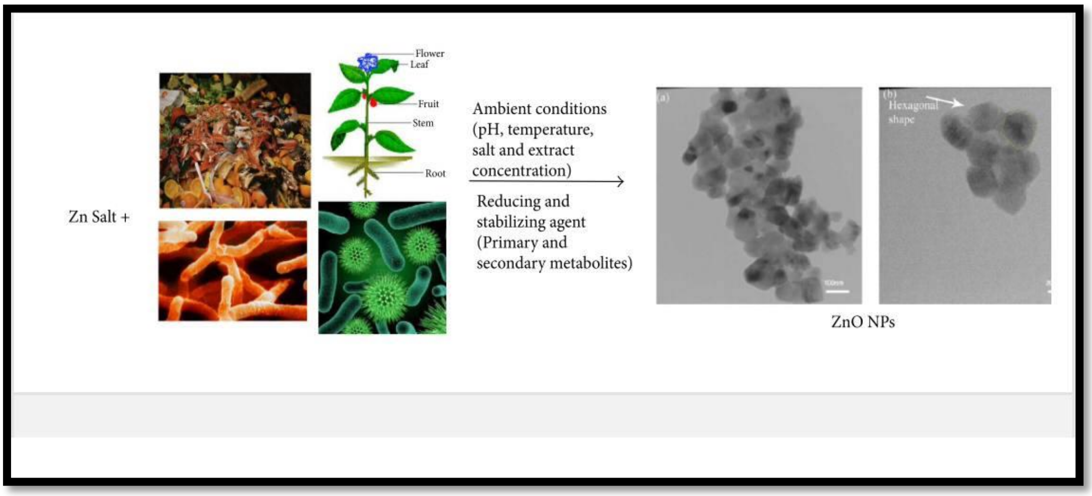


Figure (3) Green synthesis of ZnO via plants, microbes, and other routes. [26]

5.0- ZnO nanoparticles uses:

ZnO NPs have attracted intensive research efforts for their unique properties and versatile applications in transparent electronics, ultraviolet (UV) light emitters, piezoelectric devices, chemical sensors, and spin electronics [27, 28]. ZnO is nontoxic; it can be used as photocatalytic degradation materials of environmental pollutants. Bulk and thin films of ZnO have demonstrated high sensitivity for many toxic gases [29]. ZnO is currently listed as a "generally recognized as safe (GRAS)" material by the Food and Drug Administration and also used as food additive. ZnO nanostructures exhibit high catalytic efficiency, as well as strong adsorption ability, and are more frequently used in the manufacture of sunscreens. Most preferentially, among different metal oxide nanoparticles, zinc oxide (ZnO) nanoparticles have their own importance due to their vast area of applications, for example, gas sensor, biosensor, cosmetics, storage, optical devices, window materials for displays, solar cells, and drug-delivery [30–31]. ZnO NPs play some potential role in CNS and perhaps during development processes of diseases through mediating neuronal excitability or even release of neurotransmitters. Some studies have indicated that ZnO NPs affected functions of different cells or tissues, biocompatibility, and neural tissue engineering [32, 33, 34] but little information is present about the influence on CNS and CNS related diseases. ZnO NPs have been suggested to modulate synaptic transmission in vitro and to change the spatial cognition capability via enhancing long-term potentiation (LTP) in rats. It is also suggested that exposure to ZnO NPs led to a genotoxic potential mediated by lipid peroxidation and oxidative stress [35, 36]. However, due to its targeting potential ZnO NPs have potential utility in the treatment of cancer and/or autoimmunity [37].

6.0- Distinguishing Properties of Zinc Oxide Nanoparticles:

Zinc oxide nanoparticles possess the following distinguishing properties.

6.1- Physical Properties of ZnO NPs.

Zinc oxide nanoparticles have tremendous physical properties. This is worth noting that as the dimension of semiconductor materials shrinks down continuously to nanometer or even smaller scale than in this reduction some of their physical properties undergo changes known as "quantum size effects." For example, quan- tum confinement increases the band gap energy of quasione-dimensional (Q1D) ZnO, which has been confirmed by photoluminescence [38]

6.2- Optical Properties of ZnO NPs.

Intrinsic optical prop- erties of ZnO nanostructures are being intensively stud- ied for implementing photonic devices. Photoluminescence (PL) spectra of ZnO nanostructures have been extensively reported, [39]. From the photoconductivity measurements of ZnO nanowires, it is found that the presence of O2 has an important effect on the photoresponse. It was found that the desorption-adsorption process of O2 affects the photoresponse of ZnO nanowire. Upon illumination, photo- generated holes discharge surface chemisorbed O2 through surface electron-hole recombination, while the photogener- ated electrons significantly increase the conductivity. When illumination is switched off, O2 molecules readsorb onto nanowire surface and reduce the conductivity [40, 41].

6.3- Antimicrobial Properties of ZnO NPs

Antimicrobial activities of metal oxide (ZnO NPs) powders against Staphy- lococcus aureus, Escherichia coli, or fungi were quantitatively evaluated in culture media. It was observed that the growth inhibition was solely higher in biologically synthesized ZnO than chemical ZnO nanoparticle as well as other common antimicrobials. The enhanced bioactivity of these smaller particles is attributed to the higher surface area to volume ratio. The ZnO nanoparticles constitute an effective antimi- crobial agent against pathogenic microorganisms. Basically the detected active oxygen species generated by these metal oxide particles could be the main mechanism of their antibac- terial activity[41].

6.4- The antibacterial mechanism of ZnO NPs

involves the direct interaction between ZnO nanoparticles and cell sur- faces affecting cell membrane permeability; afterwards these nanoparticles enter and induce oxidative stress in bacterial cells, which results in the inhibition of cell growth and eventually cell death; the demonstrated antibacterial activity of ZnO NP recommends its possible application in the food preservation field. It can be applied as a potent sanitizing agent for disinfecting and sterilizing food industry equipment and containers against the attack and contamination with food borne pathogenic bacteria. The NPs of ZnO showed both toxicity on pathogenic bacteria (e.g., Escherichia coli and Staphylococcus aureus) and beneficial effects on microbes, as Pseudomonas putida, which has bioremediation potential and is a strong root colonizer [42].

7.0- Toxicity of ZnO in Mammalian Model

However, controversial results have been reported in the literature regarding toxicity of the ZnO in the living cells particularly in mammalian cells. Some of the reports have shown that ZnO are biocompatible and nontoxic [43-44], while some studies have recently reported both in vivo and in vitro toxicity of the ZnO on mammalian cells [45]. It can be elucidated from such studies that the toxicity of ZnO depends upon the concentration used. Vandebriel and Jong had reviewed the ZnO toxicity in mammalian model . Further, such toxicity is

important in other aspects, for example, for the treatment of cancerous, pathogenic, and leukemic T cells. Such nanoparticles are also important to overcome problems like drug resistance which is one of the major problem in the pharmaceutical industry. This is because of the nonselectivity of ZnO[46-47].

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