

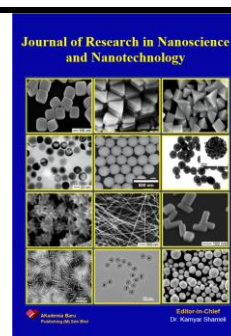


# Journal of Research in Nanoscience and Nanotechnology

Journal homepage:

<https://www.akademiabaru.com/submit/index.php/jrnn/>

ISSN: 2773-6180



## Green Route for the Fabrication of ZnO Nanoparticles and Potential Functionalization with Chitosan Using Cross-linkers: A Review

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<https://doi.org/10.37934/jrnn.3.1.125>

### ABSTRACT

Zinc oxide is of significant importance for many industries due to its versatile properties, which have been enhanced with the production of this material in the nanoscale. Recent interest in the preparation of metal oxide nanoparticles using biological approaches has been reported in the literature. This technique known as "green synthesis" is an environmentally benign process than conventional methods like physical and chemical synthesis methods. Zinc oxide nanoparticles (ZnO-NPs) have been successfully obtained by green synthesis using different biological substrates like chitosan. Chitosan is biocompatible, biodegradable polymer having exclusive physical and chemical properties. Chitosan/metal oxide nanocomposite is a promising nanomaterial with enhanced properties for multiple functionalities. Therefore, this review discusses favorable approach in the formation of cross-linked Chitosan/ZnO nanocomposites attracting significant attention in various fields such biomedical due to their unique biodegradable, biocompatible, non-toxic nature. The use of biological sources, fabrication of green synthesized ZnO nanoparticles and its applications is briefly discussed. Overall, this review is a comprehensive study for the synthesis of ZnO-NPs using biological sources counting on their features and applications.

#### Keywords:

Zinc oxide nanoparticles, Green synthesis,  
Nanocomposites, Cross-linker, Chitosan.

Received: 29 May 2021

Revised: 18 June 2021

Accepted: 26 June 2021

Published: 7 August 2021

## 1. Introduction

The nanomaterials are the materials having nanoscale dimension with less than 100 nm size ones at least in one dimension [1, 2]. Nanoparticles (NPs) are wide class of materials that include

particulate substances, with enhanced catalytic reactivity, thermal conductivity, non-linear optical performance and chemical steadiness owing to its large surface area to volume ratio [1, 3]. Nanoparticles are of great scientific interest as they bridge the gap between bulk materials and atomic or molecular structure. With the development of nanomaterials, metal oxide nanoparticles show promising and far-ranging prospect for biomedical field. As an inorganic semiconductor, zinc oxide nanoparticles (ZnO-NPs) is an attractive candidate in biomedical applications due to its large binding energy, wide band gap, crystal structure (hexagonal wurtzite), biocompatibility, non-toxicity, and anticancer properties [4, 5]. The US Food and Drug Administration (21CFR182.8991) stated ZnO as a relatively safe and biocompatible material to use in treatments of cancer, diabetes, cardiovascular disease, microbial and fungal infection, ischemic, and kidney diseases [6-9]. Variety of condition and methods have led to fabricate ZnO nanostructures with varied morphologies include nanoparticles, nanowires, nanobelts, nanotubes, nanosheets, nanorods, nanoneedles, and nanowhiskers [10]. ZnO-NPs can be fabricated through methods of solvothermal and hydrothermal [11], precipitation [12, 13], polymerization [14], laser ablation [15], sonochemical [16], and sol-gel [17, 18], microwave approaches [19]. The sol-gel procedure has gained much attention to synthesize ZnO-NPs with desirable shape modulation, physiochemical properties, and patterning of the nanostructures [18]. Green materials have been widely used for the production of various metal and metal oxide NPs. For example, *Ailanthus altissima* fruit extracts [20], phoenix dactylifera waste [21], plant *Lawsonia inermis* [22], *Punica granatum* [23], and *Justicia procumbense* leaf extract [24] have been recently used in the green synthesis of ZnO-NPs [25]. In addition, polysaccharide hydrocolloids include alginate, starches, pectin, pullulan, and gums are high molecular weight macromolecules, low-cost, and easily available to use in the green synthesis of ZnO-NPs [18, 26, 27]. Chitosan is the second most abundant polysaccharide on earth, with the production of over 100 million tons per year [28, 29]. It may be derived from chitin and is a cationic linear and natural amino-polysaccharide containing -(1-4)-linked d-glucosamine and N-acetyld-glucosamine in de-acetylated and acetylated form, respectively [30, 31]. In medically-related applications, one of the popular biocompatible and water-rich coating agents on ZnO-NPs is chitosan [32]. Owing to the bio-compatible, eco-friendly, and low cost chitosan/ZnO composites should be studied for further applications. In this study, green synthesis of ZnO-NPs and potential preparation of cross-linked chitosan/ZnO nanocomposites will be also discussed with its production leading to enhanced features.

## 2. Nanoparticles Synthesis Methods

The two general approaches that are usually used for the fabrication of nanoparticles are “top-down” and “bottom-up” approach according to the processes involved in creating nanoscale structures as shown in Figure 1. The “top-down” approach involves the thermal, chemical or mechanical disintegration of large particles of bulk metal into nanoparticles, while the more common “bottom-up” approach involves the generation of metal atoms from the reduction or decomposition of a precursor first followed by the agglomeration of the metal to produce the nanoparticles [33]. An advantage of top-down method is the possibility of mass production in the industrial environment. The main disadvantage of this approach includes long time-consuming processes, high cost of production, generation of a large size distribution of characteristics and imperfections or defects of the surface morphology generated [34, 35]. Such imperfections within the surface structure can have

a significant effect on surface chemistry and physical properties of the metallic nanoparticles because of high aspect ratio. The bottom-up approach creates nano-objects that combine the atomic scale materials (produced by the reduction of ions) and desired nanostructures. Essentially, this field of nanofabrication utilizes atoms and small molecules as the building of multi-level structures that perform different operations and amazingly promising. The bottom-up chemical methods can be done using electrochemical, templating, sol-gel process, chemical co-precipitation, nanospheric, chemical, photochemical, sonochemical, chemical vapour deposition and thermal techniques which often lead to the formation of hazardous by products [35, 36]. It can be said that bottom-up approach is commonly used for chemical and biological synthesis of nanoparticles. It is important to provide a comprehensive platform on these synthesis approaches that might be beneficial for researchers seeking development of new techniques, especially for the production of complex and multicomponent nanomaterials that could lead to advanced functional applications. Figure 2. illustrates the techniques of “bottom-up” and “top-down” approaches in the production of nanoparticles.

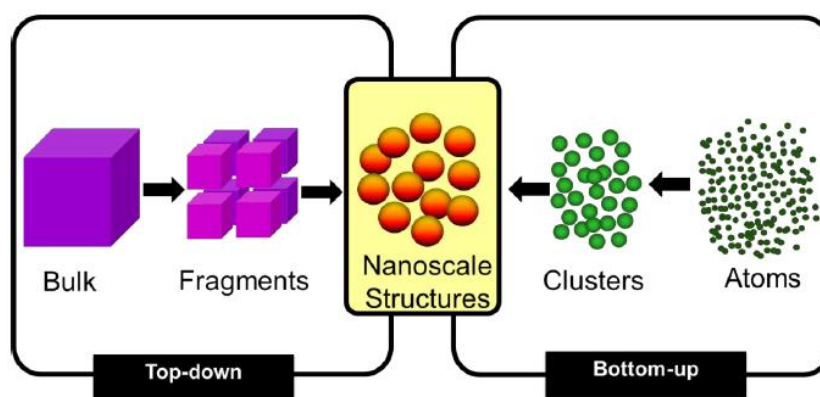


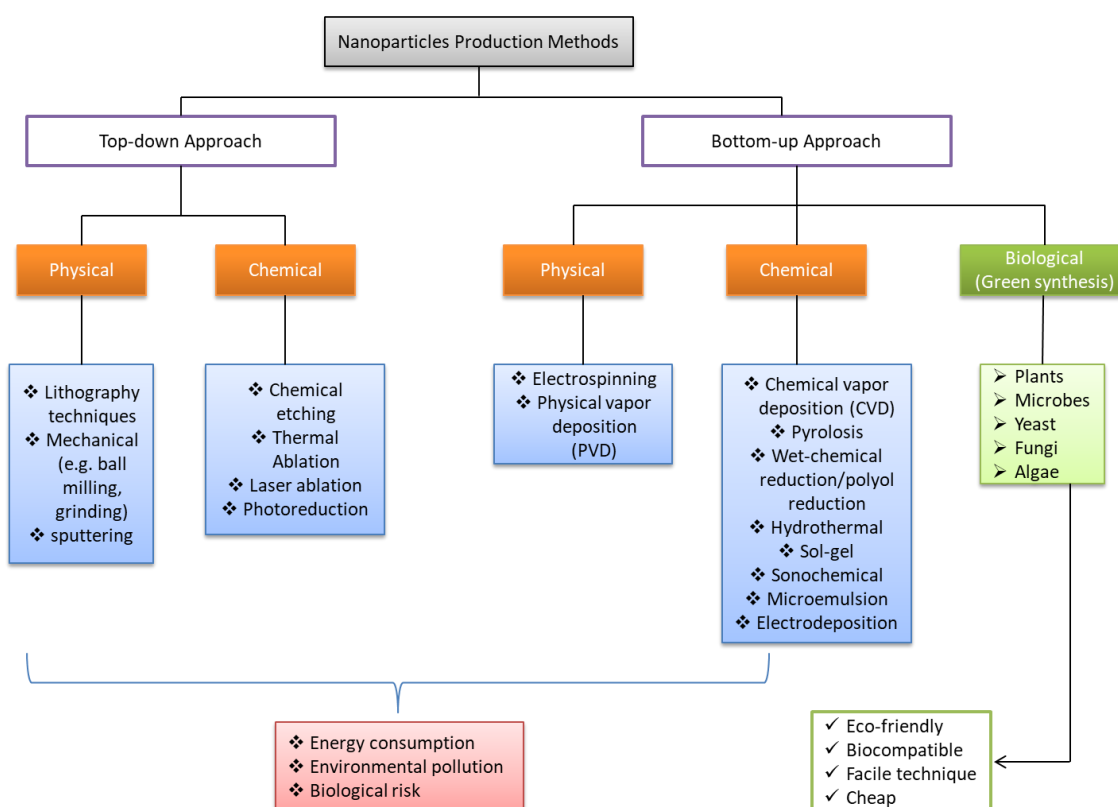
Figure 1: “Top-down” and “bottom-up” synthesis of nanofabrication [37].

### 3. Nanoparticles Synthesis Methods

Nowadays, metal and metal oxide nanoparticles are intensely studied due to their unique optical, electrical and catalytic properties compared to bulk materials. Various techniques in the manufacturing of metal nanoparticles including chemical and physical means have been developed to produce metal nanoparticles. These include chemical reduction [38, 39], electrochemical reduction [40], photochemical reduction [41], heat evaporation [42] and others. However, in most of these techniques, the organic solvents, toxic reducing agents and stabilizers used have potential environmental and biological risks, and these techniques involve more than one reactive step [43].

Biosynthesis of nanoparticles is an approach of synthesizing nanoparticles using microorganisms and plants having biomedical applications [1]. This approach is an environment-friendly, cost-effective, biocompatible, safe, green approach. Green chemistry is a set of principles or practices that encourage the design of products and processes that reduce or eliminate the use and generation of hazardous substances [44]. Current green nanotechnology practices often involve the

use of natural sources, non-hazardous solvents, biodegradable and biocompatible materials and energy-efficient processes in the preparation of NPs [44]. Therefore, the biological approach for synthesis of nanoparticles becomes important to reduce or eliminate the use and generation of hazardous substances. A vast array of biological resources available in nature including plants and plant products, algae, fungi, yeast, bacteria, and viruses could all be employed for synthesis of nanoparticles [45]. They allow large scale production of ZnO NPs free of additional impurities [1, 35]. Even though a considerable amount of research has been reported in this field, the mechanism of formation of the nanoparticles obtained by green synthesis has still to be defined and understood due to the high complexity of the biological extracts [46]. Some of the examples of green synthesized nanomaterials are listed in Table 1.



**Figure 2:** Various approached in the fabrication of nanoparticles using “Top-down” and Bottom-up” techniques.

**Table 1:** Green synthesized metal and metal oxide nanoparticles.

Type of Nanomaterials	Stabilizer	Method	Solvent	Average size	Reference
<b>Fe<sub>3</sub>O<sub>4</sub> NPs</b>	<i>Garcinia mangostana</i> (GM) fruit peel extract	Co-precipitation	deionized water	13.42±1.58 nm	[47]
<b>Ag-NPs</b>	<i>B</i>	biosynthesis	distilled water	32.7 ± 5.7 nm	[48]
<b>Ag-NPs</b>	<i>Entada spiralis</i> aqueous extract	In-situ biosynthesis	deionized water	4.74 nm	[49]
<b>Ag-NPs</b>	Green tea extract ( <i>Camellia sinensis</i> )	Biogenic route	deionized water	2.17 nm	[50]
<b>Ag-NPs</b>	<i>Berberis vulgaris</i> leaf and root aqueous extract	Facile green synthesis	-	30 to 70 nm	[51]
<b>Cu-NPs</b>	Natural honey	Facile green synthesis	double distilled water	3.81 ± 1.135 nm	[52]
<b>Cu-NPs</b>	<i>Azadirachta indica</i> plant extract	Green synthesis	de-ionized water	28-30 nm	[53]
<b>Cu-NPs</b>	<i>Cassia auriculata</i> leaf extract	Green synthesis	double-distilled water	23 nm	[54]
<b>ZnO-NPs</b>	<i>Passiflora caerulea</i> fresh leaf extract	Green synthesis	-	30–50 nm	[55]
<b>ZnO-NPs</b>	Pullulan	Sol-gel	deionized water	28.86 to 127.69 nm	[56]
<b>Au-NPs</b>	<i>Ziziphus zizyphus</i> leaf extract	Simpler and Greener method	-	3 nm	[57]
<b>Au-NPs</b>	<i>Dalspinin</i>	Greener method	deionized water	10.5 nm	[58]
<b>TiO<sub>2</sub> NPs</b>	leaf extract of <i>Trigonella foenum-graecum</i>	Biosynthesized methods	-	20 to 90 nm	[59]
<b>TiO<sub>2</sub> NPs</b>	leaf extract of <i>Jatropha curcas</i> L.	Green synthesis	double distilled water	13 nm	[60]
<b>TiO<sub>2</sub> NPs</b>	Orange peel extract	Green synthesis	deionized water	21.61nm and 17.30 nm	[61]
<b>ZrO<sub>2</sub> NPs</b>	<i>Acinetobacter sp.</i> KCSI1	Facile green synthesis	deionized water	44 ± 7 nm	[62]

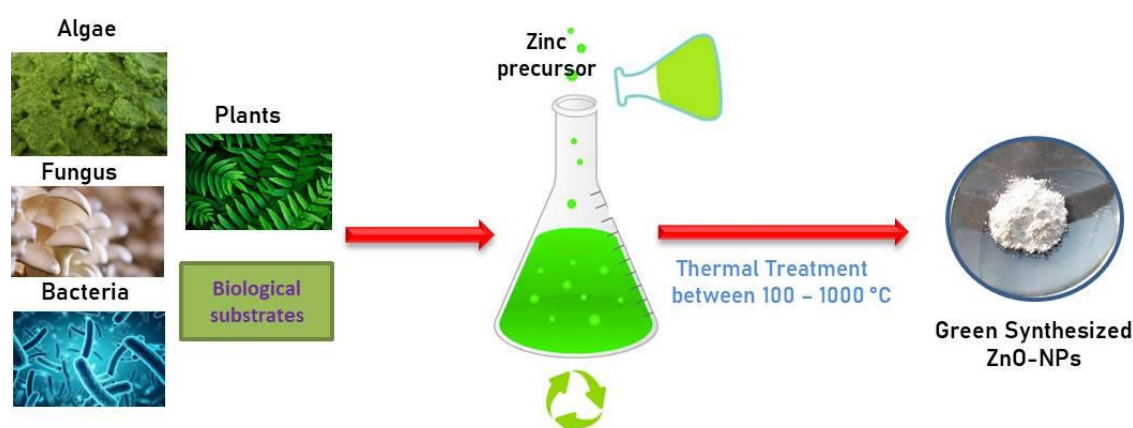
<b>MgFeCrO<sub>4</sub>-NPs</b>	<i>Tragacanth</i> gum	green sol-gel method	deionized water	17 nm	[63]
<b>ZnS-NPs</b>	<i>Stevia rebaudiana</i> extract	Green synthesis	deionized water	8.35 nm	[64]
<b>PbSe-NPs</b>	<i>Trichoderma</i> sp. WL-Go	Bio-synthesis	-	10-30 nm	[65]
<b>CdTe-NPs</b>	<i>Thevetia peruviana</i> leaf extract	Bio-synthesis	distilled water	4 –6 nm	[66]
<b>Pd</b>	Plant extract of <i>Salvia hydrangea</i>	Green Synthesis	-	9 nm	[67]
<b>Pt</b>	<i>Xanthium strumarium</i> Leaf extract	Green synthesis	-	22 nm	[68]

#### 4. Synthesis of Zinc Oxide (ZnO) Nanoparticles

Zinc oxide nanoparticles can be synthesized using a variety of methods such as chemical, physical and biological. Physical and chemical methods consist of precipitation, wet chemical, microemulsion, chemical reduction, sonochemical method, solvothermal method, pulsed laser deposition, spray pyrolysis, vapor transport and condensation, sputtering, sol-gel, gamma irradiation, microemulsion, microwave assisted irradiation, co-precipitation, hydrothermal technique [46, 69]. Yet, green synthesis of zinc oxide nanoparticles has many advantageous on chemical and physical methods.

#### 5. Green Synthesis of Zinc Oxide (ZnO) Nanoparticles

Scientists choose the green synthesis of nanoparticles using plants like fruits, roots, leaves, roots and stems and microorganisms like algae, bacteria, yeast and fungi which lead to various applications. Green synthesis of nanoparticles shows more catalytic activity and restricts the usage of hazardous and expensive chemicals. This green synthesis of zinc oxide nanoparticles has some benefits like safe, cost effective, environment benign, non-toxic, bio-compatible, and large-scale production is plausible [7, 70]. The development of this new approach and the significant interest in it is mainly related to the absence of toxic chemicals or high amount of energy applied to the biological synthesis, which makes the process more cost-effective and eco-friendly [46]. Moreover, the main advantage of this method is that the raw materials used are naturally rich in amino, carboxyl and hydroxyl groups that are often used a stabilizing or capping agents in aqueous medium, triggering the formations of nanoparticles [71]. Many available literatures indicate that the green synthesis of Zn-NPs is more environmentally friendly than the conventional physical or chemical methods used nowadays. Green synthesis of nanoparticles is a methodology for the formation of nanoparticles using plants and biopolymers which enhances its biomedical applications. Schematic illustration of green synthesis of ZnO-NPs is displayed in Figure 3. below.



**Figure 3:** Schematic illustration of green synthesis of ZnO [5].

### 5.1. Plant Mediated Synthesis of ZnO-NPs

Biological synthesis of nanoparticles employing plants and their extracts is cheap and eco-friendly technique as compared to physical and chemical procedures that are expensive and hazardous to the environment. Plants are the most common biological substrate used for the green synthesis of nanoparticles with metallic ions [46]. Plant parts like leaf, stem, root, fruit, and seed have been used for ZnO NPs synthesis because of the exclusive phytochemicals that they produce [1, 25]. This may be related to the fact that vegetal substrates are accepted to be more cost-effective, simple and less harmful than microorganisms. Plants are most preferred source of NPs synthesis because they lead to large- scale production and production of stable, varied in shape and size NPs [1].

Generally, green synthesis of ZnO-NPs using plants sources like leaves or flowers is washed thoroughly in running tap water and sterilized using double distilled water (some use Tween 20 to sterilize it). Then, the plant part is dried at room temperature followed by grinding into powder using a mortar and pestle. Next, the weighed powder and distilled water mixed to together under continuous magnetic stirring to prepare plant extract. The solution is filtered using whatman paper to obtain clear solution to be used as plant extract for further process. The specific volume of plant extract is mixed with zinc precursors like zinc nitrate, zinc acetate, zinc sulphate or zinc chloride solution. Later, the mixture is calcined at a higher temperature resulting in the formation of ZnO-NPs. The obtained ZnO-NPs are visually confirmed by colour change and the UV-vis spectroscopy was used to further confirmation. Table 2. summarizes the different plant sources that are utilized for the production of ZnO-NPs.

**Table 2:** Plant mediated synthesis of ZnO nanoparticles.

Plant Source	Description	Precursor	Size & Shape	Reference
<i>Ferulago angulata</i> (schlecht) boiss	Plant	Zinc Acetate Dihydrate	32 and 36 nm with spheroid shape	[72]
<i>Sageretia thea</i> (Osbeck.)	Leaf	Zinc Acetate Dihydrate	14 nm	[73]
<i>Plectranthus amboinicus</i>	Leaf	Zinc Nitrate	20–50 nm with spherical and hexagonal	[74]
<i>Anisochilus carnosus</i>	Leaf	Zinc Nitrate	30 and 40 nm with hexagonal wurtzite structure	[75]
<i>Limonia acidissima</i> L.	Leaf	Zinc Nitrate	12 nm and 53 nm with spherical shape	[76]
<i>Syzygium cumini</i>	Leaf	Zinc Acetate	71 nm with spherical-like shape	[77]
<i>Punica granatum</i> (pomegranate)	Plant	Zinc Nitrate Hexahydrate	32.98 nm and 81.84 nm with spherical and hexagonal shapes	[78]
<i>Punica granatum</i> (pomegranate)	Plant	Zinc Nitrate Hexahydrate	40-70 nm with spherical shape	[79]
<i>Salvia officials</i>	Leaf	Zinc Nitrate	12 nm with hexagonal wurtzite structure	[80]
<i>Carica papaya</i>	Leaf	Zinc Acetate Dihydrate	14 nm with semi-spherical	[81]
<i>Arthrospira platensis</i>	Plant	Zinc Acetate Dihydrate	30.0 to 55.0 nm with spherical shape	[82]
<i>Bergenia ciliata</i> Rhizome	Plant	Zinc Acetate Dihydrate	30 nm with flower shaped structure	[83]
<i>Acalypha fruticosa</i>	Leaf	Zinc Acetate Dihydrate	50–60 nm with Spherical and hexagonal shape	[84]
<i>Medicago sativa</i>	Leaf	Zinc Nitrate Hexahydrate	13.94 ± 1.08 nm with hexagonal structure	[85]



Green tea	Leaf	Zinc Acetate Dihydrate	30–40nm with irregular and uniform hexagonal plates	[86]
<i>Garcinia gummi-gutta</i>	Seed	Zinc Nitrate Hexahydrate	10–20nm with hexagonal irregularity	[87]
<i>Achyranthes aspera</i>	Leaf	Zinc Nitrate	30–40 nm with flake like shape	[88]
<i>Couroupita guianensis</i>	Leaf	Zinc Nitrate	5–10 nm with spherical shape	[88]
<i>Emblica officinalis</i>	Leaf	Zinc Nitrate	30-40 nm with quasi-spherical shape	[89]
<i>Azadirachta indica</i>	Leaf	Zinc Acetate	50 nm with spherical shape	[89]
<i>Mentha spicata</i>	Leaf	Zinc Acetate	11 to 88 nm with spherical shape	[90]
<i>Lagerstroemia Speciosa</i>	Leaf	Zinc Acetate	40 nm with hexagonal shape	[91]
<i>Tecoma castanifolia</i>	Leaf	Zinc Sulphate	70–75 nm with spherical shape	[92]
<i>Swertia chirayita</i>	Leaf	Zinc Nitrate	2 to 10 nm with spherical shape	[93]
<i>Populus ciliata</i>	Leaf	Zinc Nitrate Hexahydrate	60-70 nm in form of spheres	[94]

## 5.2. Biopolymer Mediated Synthesis of ZnO-NPs

The use of natural polymers in the synthesis of nanomaterials have a low cost and eco-friendly approach [5, 95]. Many natural polymers have been used in the synthesis of nanoparticles as a green stabilizer [96]. Cts is one of the promising natural biopolymer and has adapted with a suitable properties of biocompatibility, biodegradability, non-hazardous, odourless, metal ion adsorption. Chitosan's primary amine and hydroxyl groups have a very powerful affinity (like a chelating agent) to metal ion to decrease particle size and stop agglomeration [97]. Pullulan is also another biopolymer that is produced from starch by growing yeast like fungus *Aureobasidium pullulans*. The advantage of pullulan is it is water soluble. Pullulan is non-toxic, non-mutagenic, odourless, biocompatible and biodegradable [98]. Next, tragacanth gum (TG) is a natural, nontoxic and biocompatible polymer widely used as an emulsifier and thickener in the food and drug industries due to stability in a wide range of temperature and pH. There are studies applied the gum as an eco-friendly and cost effective polymer to synthesize zinc oxide nanoparticles. Another type of biopolymer is alginate, it is a naturally occurring poly-anionic polysaccharide derived and commercially extracted from brown marine algae (Phaeophyceae) [99]. As a low-cost, abundantly available, biocompatible and environmentally friendly biopolymer, it has been used as a green stabilizer as stated in numerous

studies. Last but not least, carrageenan is an eco-friendly polymer derived from a class of red seaweed. Carrageenan is known to have valuable biological functions, due to the superior gelling and high viscosity properties of the native carrageenan[100]. There are several biological properties of biopolymers such as antiviral activity, anticoagulant activity, antitumor activity, antioxidant activity, anti-inflammation and immunomodulatory activity that might bring more benefits in medical application [101]. Table 3. summarizes the various biopolymer sources that are utilized for the production of ZnO-NPs.

**Table 3:** Biopolymer mediated synthesis of ZnO nanoparticles.

Biopolymer	Description	Precursor	Size & Shape	Reference
<b>Carrageenan</b>	Red Seaweed	Zinc Nitrate Hexahydrate	49 nm with spherical shape	[27]
<b>Carrageenan</b>		Zinc Acetate		
<b>Kappa Carrageenan</b>	Marine Red Algae	Zinc Acetate	97.03 ± 9.05 nm with spherical and hexagonal shape	[102]
<b>Starch</b>	Polysaccharides	Zinc Acetate Dihydrate	10 and 15 nm in spherical shape	[103]
<b>Collagen</b>	Type 1 Collagen	Zinc Acetate Dehydrate	20 and 50 nm with hexagonal wurtzite structure	[104]
<b>Pullulan</b>	Polysaccharide Fungus	Zinc Nitrate Hexahydrate	28.86 to 127.69 nm with hexagonal wurtzite structure	[18]
<b>Agar</b>	Hydrophilic Polysaccharide	Zinc Acetate Dehydrate	20 nm in paddy shape	[105]
<b>Sodium Alginate</b>	Linear Polysaccharide	Zinc Nitrate	40 nm in spherical shape	[106]
<b>Exopolysaccharides (EPS)</b>	Microbial Polysaccharides	Zinc Acetate	10–100 nm in hexagonal shape	[107]
<b>Chitosan</b>	Linear Polysaccharide	Zinc Sulphate	20 to 150 nm, rod shaped	[108]
<b>Chitosan</b>	Linear Polysaccharide	Zinc Nitrate Hexahydrate	50.6-61.7 nm with spherical shaped	[109]
<b>Chitosan</b>	Linear Polysaccharide	Zinc Nitrate Hexahydrate	50 to 130 nm in spherical shape	[110]
<b>Guar Gum</b>	Galactomannan Polysaccharide	Zinc Acetate	35 nm in hexagonal shape	[111]
<b>Xanthan Gum and Konjac Gum</b>	Polysaccharides	Zinc Nitrate Hexahydrate	20-40 nm	[112]

<b>Gelatin</b>	Non-Carbohydrate (Polysaccharide)	Zinc Acetate	200 to 400 nm in irregular shape	[113]
<b>Gelatin</b>	Non-Carbohydrate (Polysaccharide)	Zinc Nitrate	200 to 400 nm in elliptical shape	[113]

## 6. Nanocomposites

There is a growing interest in the composites of polymers, semiconducting materials with inorganic or organic nanoparticles. Nanocomposite materials are hybrid materials of two or more materials with very dissimilar physical and chemical properties that remain separate and distinct on a macroscopic level and with one of the constituents having at least one dimension in between 1 and 100 nm size range [114]. Nanocomposites are produced to enhance the efficiency of the main matrix material by improving its physical, chemical, and biological properties [115]. This enhancement in the physico-chemical and biological properties also widens up the application areas of the newly produced nanocomposites in comparison with singly applied nanomaterials [115]. There are two components of a nanocomposite material, one is the matrix or the bulk material and other one is the inorganic nanofiller. The catalytic, optical, mechanical, electrical, thermal, electrochemical properties of the nanocomposite will differ markedly from that of the component materials [116]. Also, inorganic-organic hybrid materials play a major part within the advancement of future oriented enhanced functional materials. Interestingly, nanocomposite materials offer the opportunity to incorporate in the same host matrix multiple functions deriving from distinct types of nanocatalysts such as semiconductor nanoparticles (NPs) (i.e. TiO<sub>2</sub> or ZnO), metals, (i.e. plasmonic NPs), magnetic oxides, or carbon nanotubes and graphene [116]. The importance of nanocomposite materials is clear from the integrated development of nanomaterials with multifunctional properties of optical, catalytic, electrical, mechanical, electrochemical and thermal [117].

## 6. Cross-linked Chitosan Nanoparticles

In the last decades, chitosan has become one of the most appealing polymers in the biomedical and pharmaceutical fields [118]. For pharmaceutical applications, physical cross-linking is more promising since the cross-linking is reversible and may largely avoid potential toxicity of the reagents [119]. Chitosan nanoparticles have many advantages, including the ability to cross biological barriers, stabilizing macromolecules from degradation in the biological media, and modulating their release rate [120]. Chitosan nanoparticles has been intensively investigated as the carrier of drug delivery system, and chitosan nanoparticles have the functions of sustained and controlled release, increasing drug absorption, increasing targeting of anti-cancer drugs, reducing side effects of drug and improving drug stability and so on [121]. Chitosan promotes cross-linkage with various cross-linking agents to prepare an effective network to entrap the drug molecules [31, 122]. Chitosan carriers have the advantage of slow/controlled drug release, which improve drug solubility and stability, increase efficiency, and decrease toxicity [122]. The small size of these carriers makes them capable of passing

through biological barriers in vivo and delivering drugs to the lesion site to enhance applicability [122]. Thus, it has attracted much attention in the field of drug controlled release technology and targeted drug delivery here and abroad. Using different cross-linkers (glutaraldehyde, tripolyphosphate, glutaric acid, glyceraldehyde, formaldehyde, and genipin), chitosan micro/nanoparticles are prepared by various techniques [123]. Tripolyphosphate (TPP) is particularly attractive as ionic cross-linker, since it has the advantages of stable performance, simple process control and safety [121]. Within this frame, an important number of reports have addressed the capacity of chitosan, in solution or in the form of nanoparticles or microspheres, to facilitate the absorption of peptide/protein therapeutics by the mucosal routes [118]. Table 4. summarizes the list of produced cross-linked chitosan nanoparticles.

**Table 4:** Synthesis of cross-linked chitosan nanoparticles.

Nanoparticle	Cross-linker	Size & Shape	Application	Reference
Chitosan	TPP	321 nm, core-shell structure	Cytotoxicity	[119]
Chitosan	Sodium TPP	88.92 nm amorphous	Antibacterial	[121]
Chitosan	Pentasodium Tripolyphosphate (TPP)	-	In vivo gene delivery	[118]
Chitosan	TPP	Mean diameter around 150 nm	Pulmonary delivery	[124]
Chitosan	TPP	331 nm	Pickering emulsifiers	[125]
Chitosan	Glutaraldehyde	167–190 nm	Pulmonary drug delivery	[123]
Chitosan	Glutaraldehyde	201-233 nm	Brain targeting drug delivery	[126]
Chitosan	TPP	200 nm	Immunoadjuvant	[127]
Chitosan	Genipin, TPP	Diameter of ~100–150 nm	Antibacterial	[128]
Chitosan	TPP	<200 nm	Immunotherapy	[120]
Chitosan	TPP	100 nm	Drug loading	[129]
Chitosan	Sodium Tripolyphosphate	172.6 nm to 479.65 nm	drug delivery	[130]
Chitosan	1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide Space (EDC)	-	Bonding quality of fiber posts in root canals	[131]

Chitosan	Sodium Tripolyphosphate (TPP)	< 160 nm in spherical shape	antifungal	[132]
Chitosan	Sodium Citrate	lower than 5 nm	Drug carrier	[122]
Chitosan	Sodium Tripolyphosphate (TPP)	159.2–220.7 nm	Cancer treatment as a drug delivery	[122]
Chitosan	Cinnamaldehyde	550.1 nm and 531 nm	Anticancer activity as drug delivery	[133]
Chitosan	Cinnamaldehyde	80–150 nm	Antibacterial activity	[134]
Chitosan	Sodium Tripolyphosphate (TPP)	172–217 nm	antioxidant and anticancer activities	[135]
Chitosan	Glutaraldehyde	0.87(±0.07) nm	Au(III) adsorption	[136]

## 7. Cross-linked Chitosan/Metal Oxide Nanocomposites

Surface modification of metal oxide nanoparticles or preparation of cross-linked polymer metal oxide nanocomposites are significant phenomena for the enhanced properties of nanocomposites that will lead to multiple functionalities. To improve these functionalities, physical and chemical crosslinking is applied for the design of efficient Cts-based biopharmaceuticals. Cross-linked chitosan-based nanomaterials have also been produced using different type of organic and inorganic nanoparticles [137]. Consequently, chitosan has been modified using carbon nanotube, graphene, nanoclay, and metal nanoparticles [137]. These nanocomposites have several improved properties such as porosity, surface area, electrical conductivity, photoluminescence, tensile strength, morphology, and antibacterial and bio-properties [137]. Subsequently, these nanocomposite have been applied in several technical fields including sensors and devices, textiles, packaging, membrane technology, antimicrobial and biomedical materials [137]. Chitosan nanocomposites formed between chitosan and metal oxide via physical or chemical interaction and their applications in various areas such as medicinal, paints, and environmental fields are summarized in Table 5.

**Table 5:** Cross-linked chitosan/metal oxide nanocomposites and it applications.

Nanocomposites	Cross-linker	Size & Shape	Application	Reference
Cts/Fe <sub>2</sub> O <sub>3</sub>	Sodium tripolyphosphate (STPP)	A diameter of about 3–4 nm with spherical shape	Drug delivery	[138]
Cts/Fe <sub>2</sub> O <sub>3</sub>	STPP	3.9–4.3 nm	Magnetic properties study	[139]
Cts/Fe <sub>3</sub> O <sub>4</sub>	Tripolyphosphate/Sulphate	250-900 nm		[140]

chitosan-glyoxal/ZnO/Fe <sub>3</sub> O <sub>4</sub>	Glyoxal	Average pore size of 6-7 nm	Adsorption of organic dye	[141]
CoFe <sub>2</sub> O <sub>4</sub> /Chitosan	Glutaraldehyde	mesoporosity range 2–50 nm	Adsorption of indigotine blue dye	[142]
Cs/ZnO	TPP	size < 100 nm	photocatalytic activity	[143]
Chitosan/CuO	STPP	10–25 nm	antibacterial and swelling	[144]
Chitosan/TiO <sub>2</sub>	Genipin	Spherical shape with diameter of 40-60 nm	Antibacterial activity	[145]
n-TiO <sub>2</sub> -enabled chitosan	Copper (CuTICB)	-	photocatalytic activity	[146]

## 7. Conclusion

Numerous studies report the possibility of obtaining ZnO-NPs through a green synthesis process using a variety of plants, and biopolymers. Green sources act as both stabilizing and reducing agent for the synthesis of shape and size controlled nanoparticles. Although the complexity of biological substrates still poses a challenge to evaluate the green synthesis of nanoparticles, further investigations on the mechanism of formation of the biological synthesis of ZnO-NPs are necessary to achieve a better understanding of the chemical processes and reactions that occur during the synthesis. It seems that with the designation of the mentioned mechanism, it will be possible to control and optimize the green synthesis process, which is essential for the large-scale production of ZnO-NPs. ZnO-NPs is also obtained great attention to biomedical researchers due to several factors, especially tunable physicochemical properties such as size, morphology, surface charge, etc., that could be helpful for their medicinal applications. The FDA considers ZnO as generally recognized as safe. However, this designation is mainly for bulk substances (micron to larger size). Therefore, despite having versatile biomedical applications of ZnO nanoparticles, researchers simultaneously have concern about their toxicity in living systems. Therefore, this review also highlights the favourable approach to enhance the biocompatibility of ZnO-NPs with chitosan using different cross-linkers for multiple applications.

## Acknowledgement

This research was funded by Takasago Thermal Engineering Co. Ltd. grant (R.K.130000.7343.4B422) from the research management center (RMC) of Universiti Teknologi Malaysia (UTM) and Malaysia Japan International Institute of Technology (MJIIT).

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