Zinc oxide and gallium nitride nanoparticles application in biomedicine: A review

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Abstract— **Currently available data have a major impact on widening the applications area of zinc oxide (ZnO) and gallium nitride (GaN) nanoparticles (NPs). Being a new medical domain, nanomedicine shows a spectacular growth of published works. Thus, in this paper we aimed to provide comprehensive current information on the implementation of inoffensive synthetized ZnO and GaN nanoparticles. The articles in the PubMed database, Bethesda (MD): US National Library of Medicine, „PubMed.gov", Google Scholar Academic containing the keywords "nanoparticles, zinc oxide, gallium nitride, cytotoxicity, adhesion" were selected. From these articles it was collected and processed the information related to the applicability of ZnO and GaN NPs. Nanoparticles based on ZnO and GaN currently have a wide range of implementation in the field of oncology, antibacterial, antifungal domains. The combination of ZnO and GaN nanoparticles as adjuvants in target factor treatments shows an increased efficacy of the active substance obtained by ecological methods. The application of ZnO GaN NPs requires innovative methods to obtain beneficial results in biomedicine. Possession of clinical nomenclature for use of ZnO and GaN NPs would reduce their cytotoxic effects in practical applications.**

Keywords— **nanoparticles, zinc oxide, gallium nitride, cytotoxicity, adhesion.**

I. Introduction

The purpose of the study is to update information on the implementation of zinc oxide and gallium nitride nanoparticles in the medical field. The exponential growth of studies in the field of medicine, make these changes unnoticed by specialists in this field.

The paper highlighted the current data on the peculiarities of zinc oxide and gallium nitride nanoparticles, including in relation to the living organism which will facilitate the perception of information by medical specialists, which would increase the proposal / implementation of new nanotechnologies in the treatment of human diseases.

II. Materials and methods

The source of the information was represented by the articles in the online database PubMed (service of the National Library of Medicine of the National Institute of Health of the United States; US National Library of Medicine, National Institute of Health) PubMed [Internet]. Bethesda (MD): US National Library of Medicine, "PubMed.gov" (available at: https://www.ncbi.nlm.nih.gov/pubmed), Google Scholar Academic, where the keyword search was performed: nanoparticles, zinc oxide, gallium nitride, cytotoxicity, adhesion. The particularities of zinc oxide and gallium nitride nanoparticles, definition and description of nanoparticles with subcategories were included: risk factors, toxicity, and their application in the treatment of diseases. The results of recent studies have taken precedence over old hypotheses. The results, reproduced in several studies, or supported by data from other tests or experiments, took precedence over single studies with unconfirmed or contradictory results. The conclusions of existing literature journals were critically examined.

Subsequently, the information was systematized with the presentation of the main aspects of the contemporary vision on ZnO and GaN NPs.

III. Results and Discussion

The term "nano" is a Greek word meaning "extremely small or dwarf" with a size of one to one hundred nanometers. Nanoparticles are designated as a fixed extension between the raw material and the atomic or molecular compositions. The piezoelectric properties (a phenomenon discovered in 1880 by Jacques and Pierre Curie) of nanoparticles are of great interest to be widely implemented in medicine. The first attention to ZnO was shown in 1960 by Hutson, who remained unique until 1990. The first successful application of converting mechanical energy into electricity using ZnO NPs belongs to Wang and Song in 2006 [1–3].

Nanotechnologies bring about key changes by introducing innovative methods in electronics, biomedicine and materials science [4].

According to literature, nanoparticles are polymorphic being classified by classes, property, shape or size. The group includes fullerenes, metallic NPs, ceramic NPs and polymeric NPs. Nanoparticles have unique physical and chemical properties due to their active surface and nano size [5]. Metal oxide NPs such as ZnO have anti-inflammatory effects (through inhibitory mechanisms→ of the enzyme for the expression of nitric oxide synthesis, → release of proinflammatory cytokines, → myeloperoxidase, → NF-κβ pathway, → mast cell degranulation [6]), anticancer, antimicrobial, the property of transporting the active drug substance being synthesized by green methods [7, 8].

A special interest in the field of biomedicine is given to zinc oxide by widely discussed biocompatibility and cyto-toxicity, which is easily available in a large variety of shapes at a relatively low price [9]. The morphology of ZnO NPs depends on the synthesis process and at the nano scale can have the following shapes - rods, plates, spheres, box, hexagon, tripods, tetrapods, wires, tubes, rings, cages and flowers [10]. Zinc is an indispensable universal inorganic element used in medicine, biology and industry. The daily intake in an adult is 8-15 mg / day, of which approximately 5–6 mg / day is lost through urine and perspiration [10].

The methods that allow the production of ZnO nanoparticles with different shapes and size, are as follows [11]:

→ chemical vapor deposition;

→ precipitation in aqueous solution: hydrolysis of a Zn (II) solution, under conditions which limit the uncontrolled growth of particles, finally followed by a heat treatment to improve crystallinity;

→ hydrothermal synthesis: heat treatment of aqueous Zn (II) solutions under automatically generated pressure, using an autoclave as a reaction vessel;

→ gel solution method;

→ synthesis by microemulsions;

→ mechano-chemical processes: dry grinding with high energy [11].

Gallium nitride is a semiconductor material, which exhibit high chemical and physical stability, moreover, being biocompatible and possessing piezoelectric properties. Thus, GaN can be used in a wide range of bio-medical applications like biosensors, transducers for direct stimulation of living cells and tissues, as well as in the theragnostic of skeletal diseases, calcium metabolism and cancer[12–15].

GaN nanoparticles with shapes of rods, spheres, wires, tubes, disks, orthorhombic can be synthesized using methods as: chemical vapor deposition, hydride vapor phase epitaxy, molecular beam epitaxy, nitriding, solvothermal technique and grinding, etc. [12, 13]. GaN-based antibacterial therapy is also "Trojan Horse" due to siderophore ligands [16]. The inverse proportional relationship has been established where with the decrease of the GaN NPs diameter and the second order nonlinear optical sensitivity increases [17]. GaN NPs can be widely used in the treatment of cancer. A low concentration of GaN nanoparticles in the blood plasma has a therapeutic effect by facilitating membrane penetration, playing a crucial role in the distribution and immunity of the host [13].

Studies show (according to Table 1) that GaN NPs in combination with gold NP with in situ application at a size between 5 and 200 nm has the functionality of a thermo-transporter biosensor, electrochemical immune sensitization in cancer cells, photoelectrochemical aptasensor as a cancer biomarker [18–20]. In vitro GaN NPs activity with a size between 1 and 100 nm has a functionality to stimulate the proliferation of specific tissue cells (neurotypical, endothelial, mesenchymal stem) [14, 15, 21, 22].

Table 1 Application of GaN NPs in situ and in vitro

Size	Studies	Functionality	Method of synthesis	References
200 nm	in vitro	mesenchymal stem cell proliferation	epitaxial growth of vapor phase hydride (HVPE)	[21]
1-14 nm	in vitro	stimulation of neuro-typical cells (PC12)	chemical vapor storage	[22]
20-100 nm	in vitro	proliferation of porcine aortic endothelial cells	vapor phase epitaxial growth (HVPE)	[14]
50-100 nm	in vitro	porcine aortic endothelial cell proliferation	vapor phase epitaxial growth (HVPE)	[15]
50-10 nm	in situ	thermo-transporter biosensor in the detection of cancer cells	- // -	[19]
200 nm	in situ	electrochemical immune sensitization in the detection of cancer cells	chemical vapor deposition (hydrogen vapor deposition)	[18]
20-5 nm	in situ	Photoelectrochemical aptasensor as a biomarker of cancer	- // -	[20]

ZnO NPs (from Table 2), according to performed studies (with an average size of 45.49 nm, maximum 350.00 nm, minimum 3.50 nm)) are most often determined in hexagonal form (with an average size of 38.84 nm, maximum 97.50 nm, minimum 10.00 nm) and spheres (with an average size of

39.09 nm, maximum 300.00 nm, minimum 3.50 nm). Other shapes or combinations of them are also determined, such as rods, quasi-sphere, spheres and hexagon, heterostructure, spheres and sheets, stems.

Table 2 ZnO shapes depending on NP size

Form	Average size (nm)	Maximum size (nm)	Minimum size (nm)	References
rods	22.50	22.50	22.50	[23]
quasi-sphere	22.50	22.50	22.50	[24]
spheres and hexagon	24.00	24.00	24.00	[25]
hetorostructure	33.25	33.25	33.25	[26]
spheres sheets	350.00	350.00	350.00	[27]
stems	36.00	36.00	36.00	[28]
hexagon	38.84	97.50	10.00	[1], [3], [29], [11], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42]
spheres	39.09	300.00	3.50	[43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59]
Overall	**45.49**	**350.00**	**3.50**	

ZnO NPs (from Table 3) show different effects that are studied in situ, in vitro and / or in vivo, and especially the most frequent results are determined to be antibacterial (with an average size 45.49 nm, maximum 350.00 nm, minimum 3.50 nm) and antitumor (with an average size 60.06 nm, maximum 350.00, minimum 3.50 nm), followed by the antifungal effect (with an average size 35.94 nm, maximum 61.00 nm, minimum 20.00 nm) and antioxidant (with an average size 45.58 nm). The antileishmanial (with an average size of 25.63 nm), anti-inflammatory (with an average size of 190.00 nm) and in particular antidiabetic (with a size of 26.55 nm), antiangiogenesis (with a size of 30.00 nm) were also studied.

Table 3 ZnO effect depending on NP size

Effect	Average size (nm)	Maximum size (nm)	Minimum size (nm)	References
Cytotoxic	18.00	18.00	18.00	[1]
Anti- leishmanial	25.63	33.25	18.00	[1], [26]
Antidiabetic	26.55	26.55	26.55	[41]
Anti-angiogenesis	30.00	30.00	30.00	[53]
Antifungal	35.94	61.00	20.00	[3], [11], [30], [39]
Antibacterial	45.49	350.00	3.50	[1], [29], [44], [45], [11], [46], [30], [49], [26], [27], [54], [35], [36], [37], [39], [24], [40], [55], [41]
Antioxidant	45.58	66.25	18.00	[1], [34], [55]
Antitumor	60.06	350.00	3.50	[43], [46], [31], [47], [27], [51], [52], [33], [53], [60], [34], [36], [38], [39], [25], [40], [61], [55], [57], [58], [42], [59]
Anti - inflammatory	190.00	350.00	30.00	[27], [53]
Overall	**45.49**	**350.00**	**3.50**	

Zinc oxide and gallium nitride nanoparticles currently have a wide scope both in the field of oncology (anticancer, anti-inflammatory effect), as well as in the production of antibacterial and antifungal (antimicrobial effect) products. The combination of ZnO or GaN NPs as an adjuvant in target factor treatments shows an increase in the efficacy of the active substances. Determination of the NPs administration dose of ZnO and GaN can obtain a low toxicity by using green methods of theragnostic (in vivo, in situ).

IV. Conclusions

The application of ZnO and GaN NPs requires innovative methods to obtain beneficial results in biomedicine. Spherical and hexagonal forms of NPs are the most used, and as their size decreases, the effects are determined as antibacterial, antitumoral, antifungal, and antioxidant. Possession of detailed databases of the cyto-effects of NPs depending their shape size and surface treatment will definitely advance the practical side of nanomedicine.

Acknowledgment

This research was funded by the European Commission under the Grant #810652 "NanoMedTwin" and by the National Agency for Research and Development of the Republic of Moldova under the Grant #20.80009.50007.20

Conflict of Interest

The authors declare that they have no conflict of interest.

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