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Mimicking nature: Nanoflowers as novel materials for biomedical applications †

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Abstract: Vast advances in nanobiotechnology have been attributed to nanoflowers as some of the most promising materials. Nanoflowers are flower-like nanomaterials that possess a higher surface-area-to-volume ratio compared to other nanoparticle morphologies. Utilization of nanoflowers in biosensor platforms for detection of analytes or in drug delivery as conjugation sites has been extensively described in the literature. Biocatalysis, tissue engineering, and nanotheranostics are also among other areas of interest. In this review, fabrication, morphologies, and applications of nanoflowers in various areas of biomedicine are addressed. Current and future trends are discussed, while emphasis is also given to biocompatibility and nanotoxicity of these structures.

Keywords: nanoflowers; biomedicine; biosensors; drug delivery; tissue engineering

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1. Introduction

Even though nanotechnology is a scientific field that has only recently begun to develop, its potential was already apparent at the time when physicist Richard Feynman gave his famous speech entitled "There's Plenty of Room at the Bottom". In his talk, Feynman referred to the great margins that the laws of nature leave to control matter at the atomic level [1]. As a multidisciplinary field, nanotechnology combines the synthesis and technical applications of nanoscale materials. Nanomaterials present different properties than their bulk analogs due to their size. The uses of nanotechnology are innumerable, while its effects are noticeable on multiple levels, providing solutions to complex problems. Diverse applications can be found in scientific areas such as eletronics, cosmetics, the food industry, biotechnology, and pharmaceuticals [2–4]. In biomedicine, nanotechnology can be utilized in both the diagnosis and treatment of diseases. Various materials and nanoparticle morphologies can lead to different outcomes. Metal, metal oxides, carbon, dendrimers, polymeric, lipid, and composite nanoparticles are among a few [5]. Morphology and shape of nanomaterials can vary according to the desired needs, including rods, hexagons, cubes, spheres, and tiles [6]. Moreover, nanostructured surfaces have been used in various biotechnological products and platforms, such as biosensors [7]. Nanoflowers are a unique class of nanomaterials that have a structure that resembles the morphology of flowers resulting in a high surface-to-volume-ratio area and stability. Subramani et al., reported different names for morphologies of nanoflowers like rosette, spherical, rhombic, red blood cell-like, and rod-like, while ZnO petals were named as nanocones, nanobowling, nanobottles, nanoarrows, and nanonails by Shen et al. [8,9]. Inorganic, organic, or hybrid nanoflowers can be synthesized via various methods. Synthesis parameters such as reaction time, ph, and temperature can affect the final product [10]. Moreover, the coating and doping of nanoflowers can be adjusted [11]. Also, nanoflowers can be conjugated with other nanomaterials such as graphene or proteins and macromolecules [12–15]. Their structure makes them compelling candidates for various scientific areas such as catalysis, sensors, environmental or energy applications and biomedicine [16,17].

2. Nanoflowers fabrication methods

Inorganic nanoflowers synthesized via chemical and physical methods have been described extensively in the literature. Wategaonkar et al. synthesized TiO_2 nanoflowers via the hydrothermal method [18]. Bimetallic platinum-rhodium nanoflowers and $FeTiO_3$ nanostructures have also been produced with this method [19]. The solvothermal method has been utilized for the synthesis of core/shell nanostructures such as Fe_3O_4@MnO_2 and Ag@Fe_3O_4 [20,21]. A single-step technique called electrodeposition is used for the production of platinum and palladium nanomaterials [22,23]. Other methods include colloidal, sol-gel, sputtering, and microwave-assisted synthesis [24–27]. A more environmentally friendly synthetic strategy is the utilization of plant extracts as solvents [28]. Organic carbon nanoflowers have been produced via various techniques. These include arc discharge, ultrasound assisted pyrolysis, and chemical vapor deposition [29–31]. An immerse interest in research has been presented in the literature for the synergistic effects that hybrid organic–inorganic nanoflowers present. For that reason, various synthetic approaches have been reported. Hybrid nanoflowers are composed of metal ions and organic biomaterials such as enzymes, protein, or Deoxyribonucleic Acid (DNA). Copper, calcium and manganese ions conjugated with organic macromolecules have been synthesized [9]. The coprecipitation synthesis method has been extensively reported for these structures [32]. Other complex and hybrid structures include nanoflowers functionalized with graphene and Fe_3O_4/Au-macrophage nanohybrids [12,15].

3. Biomedical applications of nanoflowers

3.1. Biosensors

Among many uses such as imaging, biocatalysis, tissue engineering, and others, nanoflowers find application in biosensors. Biomedicine requires a quick and economical method for the detection of various analytes. Biosensors are analytical devices that detect biological responses and convert them into electrical signals. Nanoflowers have been used in biosensors due to their high surface-to-volume-area ratio. Their petals serve as ideal active sites for analyte binding [33]. Glucose has been detected by biosensors with CuS and Pt nanoflowers [34–36]. Graphene nanoflowers have detected H_2O_2 [37]. H_2O_2 has also been detected by biosensors with CuO and ZnO nanoflowers [38,39]. Other analytes reported in the literature are acetylcholine, choline, and ascorbic acid [40–42].

3.2. Theranostics and Imaging

Nanoparticles with applications in theranostics are being developed for the improvement of diagnostic techniques. For these purposes, iron oxide nanoparticles have been extensively reported as contrast agents in imaging. Fe_3O_4, $Fe_{0.6}Mn_{0.4}O$, and Fe_3O_4/Au-macrophage nanoflowers have been used in phototherapy, magnetic resonance imaging, and for diagnostic and therapeutic purposes [12,43,44].

3.3. Drug delivery

The high surface-to-volume ratio of nanoflowers enables them to be ideal nanomaterials for drug delivery applications. Drug and gene conjugation can occur in the petals of these unique nanomaterials. Doxorubicin was loaded into Au@Si core shell nanoflowers for anti-tumor therapy [45]. Lakkakula et al. synthesized organic nanoflowers for cyclodextrin drug delivery [46]. Graphene, an ideal platform for binding drug molecules, was decorated with titanate as a drug delivery system [47]. DNA hybrid nanoflowers can also act as biocompatible nanomaterials [48].

3.4. Biocatalysis

Nanoparticles' surface can act as a catalyst for various biological reactions. A hybrid nanoflower of polyphosphate kinase and $Cu_3(PO_4)_2 3H_2O$ was utilized for the generation of Adenosine Diphosphate (ADP) from Adenosine Monophosphate (AMP) [49]. Moreover, conversion of cholesterol and steroids has been reported [50,51]. Arastoo et al., produced collagen hydrolysates utilizing collagenase-$CO_3(PO_4)_2$ nanoflowers [52]. Other uses include the catalysis of toxic chemicals such as bisphenol-A, Methylene blue and other azo dyes [53–55].

3.4. Tissue engineering

Tissue engineering is a multidisciplinary scientific field that aims to study and create tissues or organs. ZnO nanoflowers have been utilized in tissue engineering for osseointegration, neuritogenesis, and angiogenesis [56]. Skin tissue regeneration has been reported by Xiaocheng et al. [57]. In this study, Cu_2S nanoflowers were incorporated into membranes for the treatment of skin wounds after surgery.

3.4. Antimicrobial activity

Antimicrobial activity can result from Fenton-like reactions on the surface of nanoflowers or from conjugated organic molecules and plant extracts [58]. Microorganisms against which nanoflowers have proven their antimicrobial activity include Staphylococcus aureus, Escherichia coli, Aeromonas caviae and Salmonella typhi [59–61]. Plant extracts that can act as antimicrobial materials are green tea extract and trigonella foenum-graecum seed extract among others [60,62].

4. Biocompatibility and nanotoxicity

Each nanostructure has a different toxicological profile, and thus, animal studies need to be done in order to ensure the safety and biocompatibility of the structures. One strategy to reduce the nanotoxicity of nanomaterials is the incorporation of nanoparticles into a core-shell structure, making the material biocompatible. Various core shell structures have been presented previously [11,45]. As in all nanomaterials, toxicity can also be induced by chemical synthesis byproducts and solvents. Utilizing green chemical synthesis methods or plant extracts as solvents can be a major solution to that problem [63].

5. Conclusion and future trends

Nanoflowers, a unique class of materials, can be synthesized via various methods, resulting in a variety of morphologies. Organic, inorganic, and hybrid nanostructures can find applications in drug delivery, tissue engineering, biocatalysis, and biosensors. Although these nanoparticles are stable, research needs to be done in order to stabilize more the final products. Also, reproducibility from batch to batch is a critical parameter in nanomaterial synthesis. Environmentally green synthesis methods also need to be studied, while emphasis has also to be given to the elimination of toxic chemical byproducts during the synthesis and the biocompatibility of structures. Finally, reduction of synthesis cost is another parameter that needs to be investigated.

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