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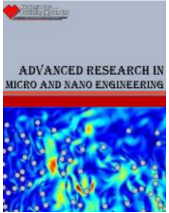

Preparation of Zinc Oxide Nanoparticles and its Cancer Treatment Effects: A Review Paper

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ABSTRACT

Zinc oxide nanoparticles (ZnO NPs) are one of the prominent metal oxide nanoparticles with significant applications in cancer treatment. Various methods of synthesis have been adopted in the production of ZnO NPs to meet its high demand. The environmental implications and economic challenges attached to most of the means of ZnO NPs synthesis have resulted in the quest for other alternatives with environmental and economic benefits. Recently in nanotechnology research, synthesis of nanoparticle from green chemistry pathways has been preferred due to its natural biological reduction property which reduces the utilization and exposure of toxic chemical to the environment when compare to physical and chemical methods. Among the different inorganic nanoparticles, ZnO NPs attracts more attention due to its, large bandwidth, high excitation binding energy, simplicity, easy fabrication, bio-safe, non-toxic, biocompatible, eco and environmental friendly. Zinc oxide nanoparticle is readily soluble in biological fluids and tends to aggregate easily under different physiological condition. But physicochemical properties of the nanoparticle have an impact in the bioavailability. This review described the summary of the recent advances in the synthesis, characterization techniques, and applications of biosynthesized ZnO NPS in cancer treatment.

Keywords:
Zinc oxide nanoparticles, synthesis methods, cancer treatment

1. Introduction

Recently, nanotechnology has become the center of research interest for its potential to manufacture and control materials on the scale of nano-size [1][2]. It deals with materials having a nanoscale dimension in the range of 1 to 100 nm [3][4]. Nanomaterials display distinctive property and features having extremely small size and larger surface area which makes them highly valued than their bulk materials itself [5][6]. Metal oxide nanoparticles have received substantial research attention due to their low production costs, stability and extraordinary magnetic, electrical, optical and catalytic properties for a wide range of applications including medical [7][8][9].

Zinc oxide nanoparticles (ZnO-NPs) is interesting due to their unique properties including high photosensitivity physical and chemical stability, high thermal conductivity, non-toxicity, large excitation binding energy (60 meV) as well as wide band gap (3.37 eV) [10][11]. It has numerous applications in various areas such as pharmaceuticals, agrochemicals, perfumes, dyes, petroleum,

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and biology due to its low toxicity in vitro and in vivo. Next to these applications, ZnO-NPs are likewise used in biomedical applications including anticancer [12], antibacterial [13], antioxidant [14], anti-inflammatory [15], drug delivery [16] and antifungal [17] uses due to its high biocompatibility, and stability under harsh environmental conditions. Numerous available researches reported on the preparation of zinc oxide nanoparticles (ZnO-NPs) using various methodological approaches like solvothermal and hydrothermal synthesis [18], precipitation [19], polymerization method[20], laser ablation [21], microwave irradiation [22], wet chemical method [23], a photochemical method [24], sonochemical [25], and sol-gel methods [26]. Yet, physical and chemical methods suffer various downsides such as usage of hazardous and toxic chemicals, high energy demand, and costly high which limits their biomedical applications. Therefore, alternative green synthesis of ZnO-NPs to conventional methods has emerged which is cost-effective, less toxic, eco-friendly, biocompatible, and highly efficient using biopolymers [27][28].

2. Preparation Methods of Zinc Oxide 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, a hydrothermal technique [29][30]. Yet, green synthesis of zinc oxide nanoparticles has many advantages on chemical and physical methods. Some of the preparation methods will be discussed here.

2.1 Microwave Assisted Irradiation

Microwave irradiation synthesis has been popularly used in the fabrication of zinc oxide nanoparticles due to its advantages over conventional methods. Using this method enhances higher yields, reaction rates, improved purity, ease of workup after the reaction in an eco-friendly manner than the traditional methods. To prepare ZnO nanoparticles 200 mL aqueous solution of 25mM Zn(NO3)2 was prepared [31]. Later aqueous solution of ammonium hydroxide (28% NH3) was added until the pH reaches 12 [31]. Next ZnO-seeded paper of 4 cm by 5cm was soaked in the prepared zinc nitrate solution and placed inside the microwave oven (General Electric Company, JE12340WPSL, China) set at 180W and 450W. Lastly, the substrate was removed from the growth solution, rinsed with deionized water several times, and dried at 90 °C for 6 hours. Microwave synthesis has the ability to heat either the solvent or the precursor molecules for nanomaterials preparation selectively.

2.2 Sol-gel technique

Sol-gel synthesis is introduced by Spanhel and Anderson in 1991, which uses a zinc precursor salt (nitrate, sulphate, chloride, etc.) where condensation and hydrolysis take place. In this method, the sol/solution was stirred until the aqueous solvent is completely removed; leaving a gel-like product. After, this solution will be exposed to thermal treatment under annealing temperatures up to 1000 °C min until it turned into fine powder form [32]. The white color ZnO-NPs powder was then stored at room temperature at about 25 ^{0}C for future experiments [33]. It is an easy way to prepare various sizes and to have relatively higher purity. Most of the studies reported the synthesis of ZnO-NPs in biopolymer in order to increase the stability of the product. Here, a possible schematic illustration of the synthesis of ZnO-NPs in biopolymer is drawn.

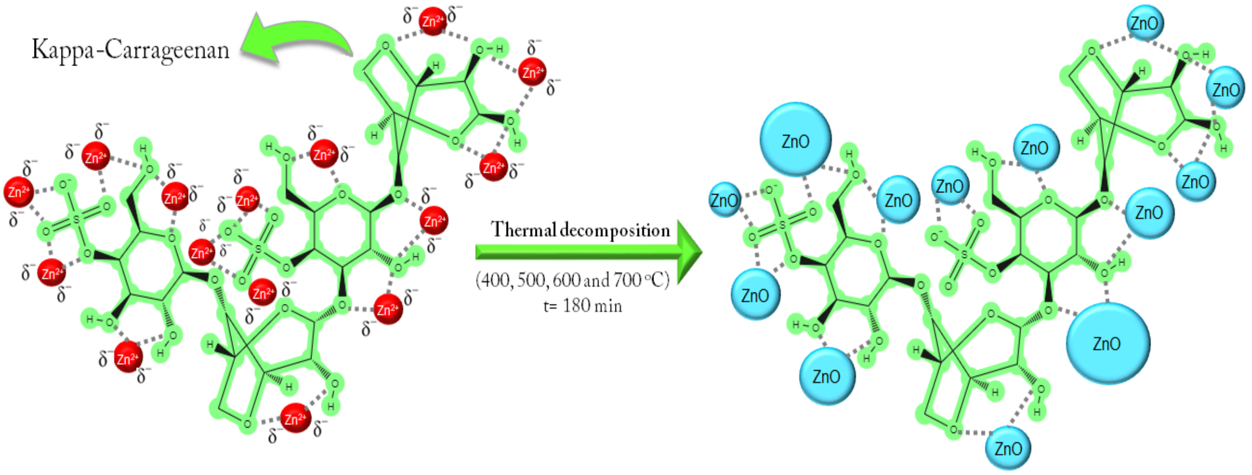

Fig. 1. Schematic illustration of Zn^{+2} ions with the main compounds found in carrageenan to synthesize ZnO-NPs

2.3 Microemulsion

This method is one of the ideal techniques for the fabrication of inorganic nanoparticles, yet the mechanism of nanoparticle formation in the micro-emulsion is a complex process to understand. Some researchers have introduced a mechanism for nanoparticle synthesis in microemulsions in water-water or water-oil. Microemulsion material consists of reactants mixed together, exchange of reactants occurs during the collision of nano-droplets resulting in the nucleation growth and formation of final nanoparticles surrounded by water or stabilized by surfactants. For instance, microemulsions were prepared in the ratio of 1:1 mixing Tween 80 to form an organic phase [34]. Then, the 0.5 M aqueous solution of zinc acetate was added as a zinc precursor and mixed together under magnetic stirring at 1200 rpm for 5 min and stored for 24 hr at room temperature [34]. The 1.0 M aqueous solution of sodium hydroxide, NaOH (97.0% purity) added to the above solution as a precipitant agent. The mixtures were kept at 60 °C and stirred at 1200 rpm for 5 min. Afterward, the mixtures were consecutively washed by centrifugation at 7500 rpm in water, acetone, and hexane, in order to separate the oil and surfactant residues from the precipitate, as well as water-soluble salts resultants of the reaction. Finally, ZnO-NPs were obtained after calcination at 800 °C for 2 h.

2.4 Laser Ablation

The pulsed laser method is another process of synthesizing ZnO-NPs by removing material from a liquid solution irradiating it with a laser beam. The material is heated by the absorbed laser energy where it evaporates or sublimates. Usually, the material is converted into plasma at high laser flux. For example, to produce nanoparticles zinc metal is mixed with distilled water in a beaker where the water level is 5 mm above the metal target, approximately 95 ml of water. ZnO nanoparticle solution was obtained by the irradiation of zinc metal with Ytterbium fiber laser (IPG Laser: YLP-1-100-20-20-HC) which operated with the following parameters at 1064 nm wavelength, 7 ns pulse duration, 20 Hz, and 150 ml [35]. The initial powders formed by ablation were additionally heat treated in a SNOL 6.7/1300 muffler furnace (Litva) in atmospheric air at 300 and 500°C for 4 h at a heating rate of 10°C/min to produce ZnO nanoparticles [35].

2.5 Hydrothermal Synthesis

This method has been generally appreciated, accumulating consideration from researchers and technologists from various disciplines. It was first utilized by British geologist Roderick Murchison (1792–1871) to portray the activity of water at raised temperature and pressure in achieving changes in the earth's crust prompting the production of rocks and minerals. The hydrothermal technique has been successful for the synthesis of significant solids, for example, microporous crystals, chemical sensing oxides, superionic conductors, complex oxide ceramic and fluorides, electronically conducting solids, magnetic materials, and luminescence phosphors. It is likewise a route to exceptional dense material, including nano-meter particles, gels, distinguished helical and chiral structures, thin films, and especially stacking-sequence materials. For example, in order to synthesize ZnO NPs using the clove hydroalcoholic extract, different amounts of zinc nitrate (2–6 g) were added into various amounts of the obtained clove extract (10–20 mL) and placed into a laboratory autoclave set at a temperature of 121°C and a pressure of 1.5 atm for 15 min [36]. Later, the mixture solutions containing ZnO NPs were decanted into ceramic crucible cups and placed into the laboratory furnace adjusted at 350°C for 2 h to result in a pale yellow powder of ZnO NPs [36]. One of the advantageous of the hydrothermal synthesis is that it is an easy process to control the size, shape distribution, and crystallinity of the final product through adjustment of the parameters, such as reaction temperature, reaction time, solvent type, surfactant type, and precursor type. Moreover, most materials can be made soluble in a proper solvent by heating and pressuring the system close to its critical point.

2.6 Sonochemical Method

The sonochemical method has been studied in the synthesis of zinc oxide nanoparticles. Acoustic cavitation and chemical influences of ultrasound are two main concerns in the sonochemical method. It is another technique used in producing new materials with a complex design by high-intensity ultrasound without applying high pressure and temperature within a short period of time. The irradiation of ultrasound gives high acoustic waves and bubbles or cavities with swing bringing about the possible application of ultrasound strength effectively to produce the nanoparticles with the appropriate formation and small size. Various studies are done in the synthesis of zinc oxide nanoparticles. For example, varying amounts of $ZnCl_2$ (1.5 g to 18.5 g) were added into a beaker to get the total volume of 100 ml of solution [25]. The solution was sonicated for 5 min until it became a homogenous solution. Different amount of NaOH granules (3.3 g to 11.7 g) was added into the running solution [25]. For further completion of the reaction mechanism, the solution was then sonicated for various time intervals (19.7 min to 70.2 min) based on CCD under ultrasonic probe homogenizer (Bandelin Sonopuls HD 3200, Bandelin Electronic GmbH & Co. KG, Berlin, Germany, 20 kHz, 200 W, 50% efficiency). After the completion of the sonication process, the resulting white flocculates were washed five times with ethanol to remove the excess amount of trashes and impurities. The successful synthesis of zinc oxide nanoparticles is obtained after centrifugation at 4000 rpm for min.

2.7 Gamma Irradiation

Gamma irradiation is one of the favored techniques for the synthesis of the metallic nanoparticle. It is an easy, cost-effective technique and uses less hazardous precursors such as water or ethanol. Moreover, it does not require high energy temperature and limits waste. The radiolytic decrease has been demonstrated to be a powerful tool in the fabrication of mono-sized and highly dispersed metallic clusters. The essential impacts of the collaboration of high-energy gamma photons with a solution of metal ions are the excitation and the ionization of the solvent. The effect of gamma ray irradiation has been studied on the structural and optical properties of zinc oxide nanoparticles. The SEM images displayed that the gamma irradiation of high dose lead to increase in grain size while decreased at a low dose [37]. The optical absorption spectra of ZnO are also obtained in the wavelength range 200–800 nm before and after irradiation. The band gap is increased at the high dose of gamma radiation and decreased at a low dose [36].

2.9 Co-precipitation

This method involves the simultaneous occurrence of nucleation, growth, coarsening, and/or agglomeration processes. Nucleation is a key step in the formation of a group of small particles. During the nucleation process, controlling the pH value is very significant. Because nanoparticles grow faster, makes it difficult to control the particle size while the pH value is above 10. Metals formed from aqueous solutions, through reduction from non-aqueous solutions, electrochemical reduction, and decomposition of metal-organic precursors while oxides formed from aqueous and non-aqueous solutions. A recent study showed the synthesis of ZnO NPs using the co-precipitation method. Firstly, two solutions of 0.1 M of zinc acetate hexahydrate and 0.2 M of NaOH are prepared by dissolving them in deionized water [38]. Then these two solutions into one beaker and stirred at 750 rpm for 2 h under a temperature of 60 °C [38]. Once the transparent solution became white milky, the centrifugation was applied at 4500 rpm for 2 min, and a white product precipitated. The precipitate product was then washed with de-ionized water and then with acetone. ZnO NPs in the form of powder were obtained by drying the product using the laboratory conventional oven at 75 °C for 6 h 9 [38] [39].

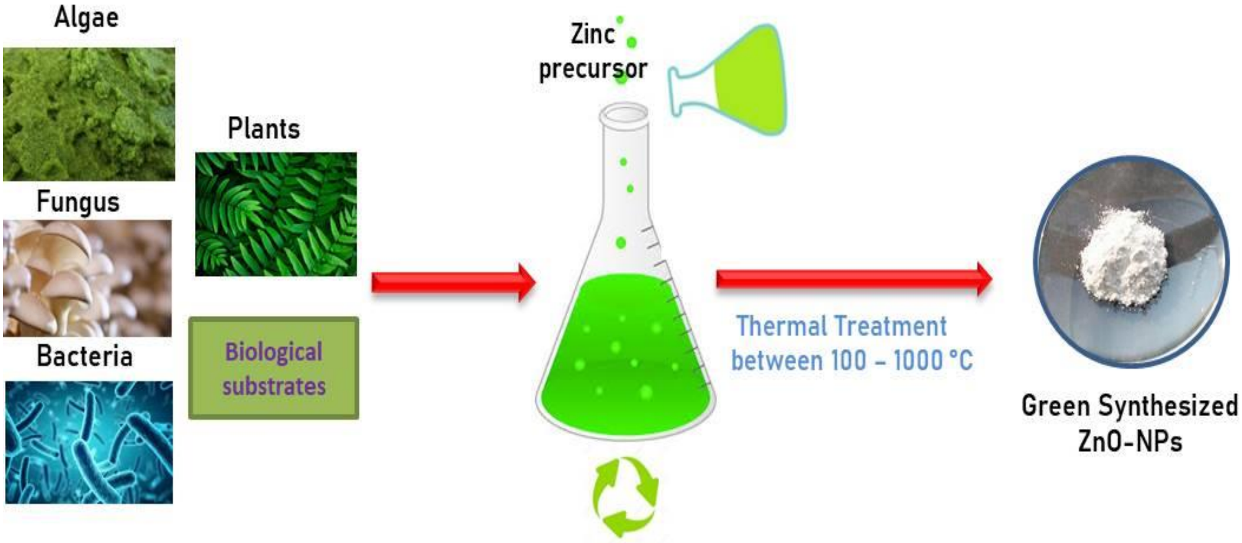

Fig. 2. Schematic illustration of green synthesis of ZnO-NPs.

2.10 Green Synthesis

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 leads to various applications [39]. 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 a safe, cost-effective, environmentally benign, non-toxic, bio-compatible, and large-scale production is plausible [39][40].

3. Cancer Treatment Effects

Cancer statistics displayed 18.1 million new cases across the world in only 2018 alone [41]. Cancer is a state of uncontrolled malignant cell proliferation and invasion. Cancer takes lives of people mercilessly [42]. It is generally treated by radiotherapy, chemotherapy and surgery in the past for a long while. Albeit every one of these treatments appear to be successful for killing cancer cells in principle, these non-selective treatment techniques additionally present a great deal of side effects [43]. With the merge of nanotechnology, nanomaterial based nanomedicine with high biocompatibility, effective surface functionalization, drug delivery capacity, and cancer targeting has exhibited the possibility to overcome these side effects. Zn^{+2} is an essential nutrient for adults, and ZnO nanomaterials are considered to be safe in vivo. Recently, the application of ZnO as anticancer agent is of great interest in the development of biomaterials in the field of microbiology because of its stability under harsh environment conditions, high biocompatibility, fast electron transfer kinetics and longer life than organic-based disinfectants [44]. Studies have proven that ZnO is fatal to cancer cells [45]. ZnO nanoparticles can generate reactive oxygen species (ROS) when reacting with the cell membrane lipids and show higher toxicity against cancer cells in vitro [46]. As the US Food and Drug Administration (FDA) has recognized bulk ZnO as a generally recognized as safe (GRAS) substance, ZnO-NPs larger than 100 nm are considered to be relatively biocompatible, which supports their use for drug delivery [47] [48]. Various studies also have been done on the positive attitude of ZnO-NPs against cancer cells.

In terms of cancer treatment, ZnO and ZnO immersed in biopolymer have exhibited high anticancer against human breast cancer cell (MCF-7 cell line) [46], AGS gastric cancer cells [49], Human Cervical cancer (HeLa) [27], human colon cancer HCT-116 [12], colorectal cancer (HCT116) [41], human colorectal adenocarcinoma cells (Caco-2 cell line) [50]. Yet, researchers concluded that the effectiveness of biosynthesized ZnO-NPs as an anticancer agent was dose-dependent, meaning that increased concentration of ZnO-NPs increases its efficiency against cancer cells. The usage of nanoparticles in targeted drug delivery has been an exciting research opportunity for effective cancer treatment. Targeted drug delivery on cancerous cells will reduce the dosage of drugs for treatment and its other side effects. The biodegradable properties and low toxicity of ZnO NPs have increased their usage in cancer drug delivery compared to other nanoparticles.

An ideal anticancer strategy is to target both cancer cells and the tumor microenvironment due to the complexity of cancer. A study reported that zinc oxide nanoparticles (ZnO NPs) were able to target multiple cell types of cancer, including cancer cells, cancer stem cells (CSCs), and macrophages, and simultaneously perform several key functions, including inhibition of cancer proliferation, sensitization of drug-resistant cancer, prevention of cancer recurrence and metastasis, and resuscitation of cancer immune-surveillance [51]. Proposed mechanism of ZnO-NPs as a multifunctional and multi-target anticancer nanomedicine is exhibited in Figure 3.

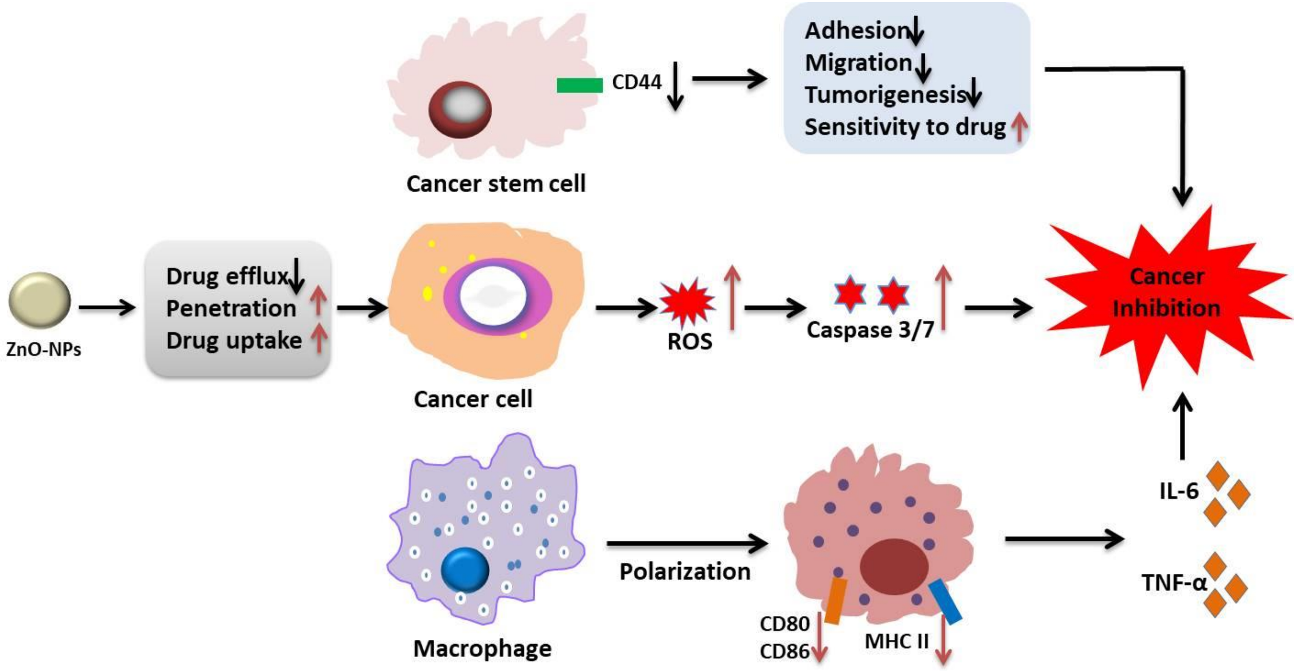

Fig. 3. Proposed mechanism of ZnO NPs that can be used as a potential multi-target and multi-functional anticancer nanomedicine.

A study also reported that ZnO-NPs could work as a pH-dependent drug carrier and displayed enhanced cellular uptake and tumor spheroid penetration [51][52]. ZnO-NPs could effectively down-regulate CD44 expression of cancer (stem-like) cells to inhibit cell adhesion, migration, and tumorigenesis, as well as sensitize drug treatment. These research results proved, ZnO NPs might have great potential to be a multi-target and multi-functional nanocarrier and nanomedicine for anticancer research.

4. Conclusions

Zinc oxide nanoparticles have gained significant interest due to their unique chemical and physical properties and are applicable to diverse areas. Various preparation methods of nanoparticles have been developed and they are suitable for the synthesis of nanoparticles in different sizes and shapes. The methods that were discussed include gamma irradiation, sol-gel, co-precipitation, sonochemical, hydrothermal, laser ablation, microemulsion, microwave-assisted irradiation, and green synthesis. Green synthesis of zinc nanoparticles has gained much importance recently due to its biocompatible and eco-friendly nature. Green sources act as both stabilizing and reducing agent for the synthesis of shape and size controlled nanoparticles. ZnO-NPs can be characterized using various tools such as XRD, UV-vis spectroscopy, FTIR, TEM and SEM for the confirmation of successfully produced ZnO-NPs. The outcome of this study will hopefully serve as a guide to anyone intending to conduct research on a similar field of interest. Moreover, the green synthesis of zinc oxide nanoparticles is greatly applicable for cancer treatment due to their non-toxicity and biocompatibility.

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