ISSN : 1001-1781
Journal of Clinical Otorhinolaryngology, Head, and Neck Surgery

A REVIEW OF GOLD NANOPARTICLES (GNPS) IN THE DEVELOPMENT OF CANCER THERAPY

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Abstract

Global cancer therapy (GLOBOCAN) estimates that 18 million new instances of cancer are diagnosed each year in the world. The three main types of cancer treatment are chemotherapy, radiation, and surgery. Patients are now being treated with the maximum tolerable dose. One of the primary problems with both radiation and chemotherapy is normal tissue toxicity, so it will be crucial to include the advancement of contemporary nanoparticle-based treatments. While local radiotherapy dose can be increased by directing the GNPs to the tumor, the Gold Nanoparticle (GNP) based systems are very helpful in further improving chemotherapy through controlled releases of chemotherapeutics. In the past two decades, more than 20 therapeutic products based on nanotechnology have been approved for use in clinical trials. The major goal of this review article is to determine how we might expedite the practical application of GNP-based therapeutic systems to decrease

typical tissue toxicity while raising the treatment's value. Future cancer treatments will change thanks to nanomedicines in a better way with fewer side effects.

Keywords: Chemo radiotherapy, Gold nanoparticles; Radiation; Drug delivery system;

Introduction

Global attention has been drawn to the development of novel NPs in chemistry and their distinct applications in the treatment of various human infections [1]. With many unused applications in medical research and prescription, nanotechnology is essential for the delivery of medicinal ingredients. NPs have a wide range of applications in nanomedicine, including cancer treatment, research methodologies, and drug formulations [2]. The choice of NPs for cancer therapy is strongly favored by their specific physicochemical characteristics, which hold promise for future advancements in the treatment of infections in cancer therapy with low adverse effects. Because of its greater size to volume ratio, NPs units utilized in nanotechnology have wholly novel or advanced properties and range in size from 1.0 nm to 100 nm [3].

As a new platform for cancer therapy to a specific target areas, metal NPs are the subject of inquiry and determination. For specific target areas in cancer therapy, nano carriers are cutting-edge instruments. Numerous distribution resources, such as nanorods, nanopolymers, nanodendrimers, and nanoliposomes, have been developed over the years using a variety of NPs. Researchers are revealing the enormous therapeutic potential of nanoscale techniques by understanding how the materials behave perversely at a specific cell or component [4]. Even though the vast majority of the research is still in its early stages, scientists are developing fresh ways and creating inventive tools for the core study fields of drug synthesis, drug carriers, target indications, toxicity reduction, and tool optimization [5,6].

Gold nanoparticles in particular have a special application in the treatment of cancer. Additionally, it has been explained that GNPs have unique synthetic and somatic properties for carrying and releasing therapeutic agents [7,8]. The main advantage of GNPs as a drug carrier is that the gold center is essentially latent and safe; in addition, the choice of GNPs is supported by ease of blending, and their position of functionalization, for the most part, completes thiol linkages. The ability of somatic traits to trigger medicine discharge [9] at a distant location is most obvious from their image.

Nanoparticles of gold (GNPs)

One of the earliest metals to come into view is gold. However, there are a few thousand years between the investigation's account and its scope. Early documentation of colloidal gold may be found in writings by Indian scholars, Chinese researchers, and Arabic scientists who sought to produce the substance as soon as the fifth and fourth centuries. For therapeutic and other uses, scientists employed colloidal gold. All chemistry research facilities in Europe investigated and used colloidal gold.

Functionalized Gold Nanoparticles (GNPs) with organized optical and geometrical characteristics have been the focus of research in a number of medical fields, including biosensors, various immune systems, experimental clinical sciences, genomics, laser therapy of tumors and cancer cells, drug delivery, antigens, and DNA, scanning, imaging, and control of cancer cells and cancer tissues with the use of cutting-edge indication methods [10].

To transport medication particles to identified target cells, GNPs have been recognised as an appealing candidate. Due to their amazing qualities, particularly in the transportation and release of drugs to their target cells, GNPs were chosen as an excellent candidate for the delivery of therapeutic agents. Efficiency of their discharge at the location is crucial for successful treatment, and therapeutic particles released must be substantially smaller in size encased in drug particles or in big biomolecules, such as amino acids, nucleic acids, RNA, or DNA [11].

Due to their biocompatibility and inertness, GNPs typically have an extraordinarily high surface-to-volume ratio and can undoubtedly be functionalized with a wide range of other functional groups. As a result, they can play a crucial role in the medical field as adjuvants, reducing the toxic effects, increasing the immunogenic effects, and providing the storage stability of medications and other drugs related to vaccinations, as well as possessing the excessive potential [12].

The GNPs have gained the most popularity as a result of their success in the delivery of drugs and in the treatment of cancer. Due to their expertise in the distribution of amino acids, proteins, nucleic acids, and gene therapy in vivo cure and symptoms, GNPs have developed their own path from discovery to therapy in today's drugs. [12]. In order to make GNPs particular to disease zones and enable them to selectively interface with other cells or biomolecules, outer functionalization of GNPs is crucial for biomedical applications. The following GNPs have intriguing properties, such as measure- and figure-subordinate visual and electronic attributes, a high surface zone to sum proportion, and surfaces that can be quickly changed with the ligands holding valuable assemblies, such as amines, phosphines, and thiols, which prefer gold faces [14]. Extra moieties such as antibodies, amino acids, proteins, and dinucleotides are used to report the common usefulness through techniques for these practical groups to attach the ligands [4]. GNPs' outstanding somatic and synthetic properties are the basis for their broad range of applications. According to size, shape, and molecular structure, the surface plasmon vibrations of GNPs [2], which relate to connected excited conductive electrons and are limited within a broad region, from visible to infrared (IR) area, regulate their optical properties specifically. Different GNP shapes and their applications are shown in Figure 1.

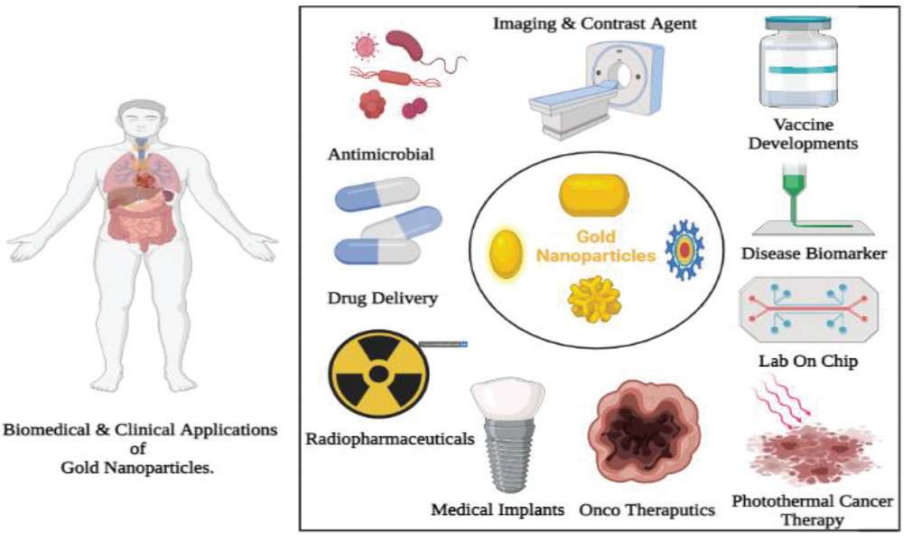

Figure 1: Biomedical applications and different shapes of GNPs.

Methods for the synthesis of gold nanoparticles

For the most part, the following procedures have been used to create gold nanoparticles (GNPs):

Chemical strategies: The most common chemical method for creating GNPs is the well-known Turkevich method, which is also one of the most promising approaches when compared to others. In this method, the citrate [15], ascorbic acid [16], and tannic acid [17] are used as mild reducing agents to reduce the Au+3 ions. According to Figure 2, the Turkevich approach is used to create the biocompatible and compact GNPs. For the synthesis of GNPs during this process, it is vital to regulate the parameters such as pH, temperature, and concentration [18]. Brust and Schiffrin introduced their method, known as the Brust-Schiffrin method, in 1944. The thermally stable, air-stable, low-dispersion GNPs are simple to make using this technology. Using tetraoctylammonium bromide (TOAB) as the phase-transfer agent and reducing NaBH4 in the presence of dodecanethiol, AuCl4 was transferred from an aqueous solution to toluene in this procedure. When reducing chemicals are used, the organic phase's orange color turns deep brown [19].

The synthesis of GNPs with a limited size distribution and a diameter of 5–40 nm can also be accomplished by the seeding growth approach. By adjusting the ratio of seed to metal salts, the particle size may be adjusted, allowing the creation of particles with a size range of 5 to 40 nm [20]. Because it is quick, easy, and affordable, this method has benefits [21].

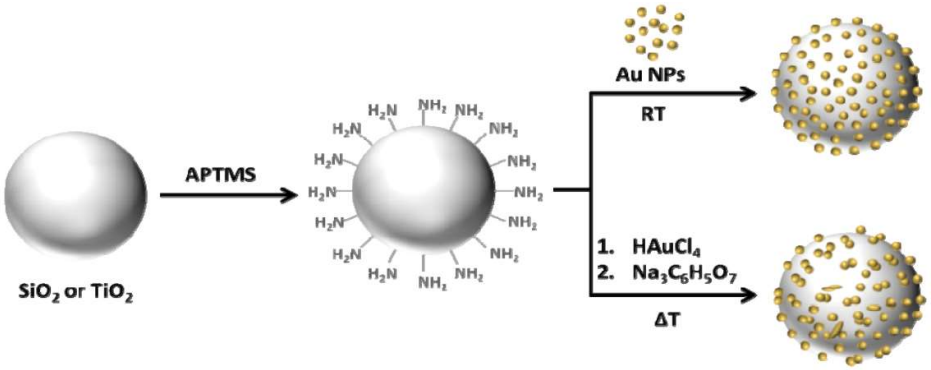

Figure 2: Schematic diagram for the synthesis of gold nanoparticles by Turkevich method.

Biological approaches:

The most popular methods for creating metallic nanoparticles are chemical approaches. Their use is constrained by the high cost of reducing and stabilizing agents. Additionally, the chemical methods used to create nanoparticles may have toxic effects in biomedical applications [22]. Therefore, it is necessary to create simple, affordable processes for creating nanoparticles without using any hazardous chemicals. The creation of nanoparticles using biological processes has recently attracted interest as an environmentally benign and green technique. Nanoparticle production in biological processes is often carried out by microbes, plants or plant extracts, and enzymes [23]. Because they are less toxic, more affordable, and environmentally friendly, plants are now preferred over other materials for the synthesis of nanoparticles. Azadirachta indica [22], Aloe Vera [24], Medicago sativa [25], Cinnamomum camphora [26], Coriandrum sativum [27], Pelargonium graveolens [22], Terminalia catappa [28], and lemongrass [22] are some of the plants that have been employed in recent years to produce nanoparticles through biosynthesis.

The synthesis of GNPs by the use of plant extracts such as Memecylon umbellatum [29], Citrus limon, Citrus reticulata and Citrus sinensis [30], Memecylon edule [31], Terminalia chebula , Nyctanthes arbor-tristis [32], Mangifera indica [33], Cinnamomum zeylanicum [34], Piper pedicellatum [35], Cochlospermum gossypium [36], Brevibacterium casei [37] and Macrotyloma uniflorum [38].

GNPs between 5 and 15 nm can be created using the extract of Zingiber officinale. In the synthesis of GNPs, Zingiber officinale serves as both a reducing and a stabilizing agent [39].

Cancer therapy

In the past few years, significant progress has been made in the synthesis and uses of GNPs for the treatment of cancer. Due to their surface activation and photothermal heating capacity, GNPs are particularly suitable to thermally destroy the cancer cells [1]. The

multidisciplinary subject of tumor nanoscience has many applications in the treatment of cancer, including cancer cell detection, molecular imaging, bioinformatics, and target therapy [40]. Chemotherapy, radiation therapy, and surgical treatment are common techniques to tumor therapy. Due to their unique qualities [41] as their capacity to interact with various medications, retention in tumor tissues, light absorbance in near-infrared light, and their interaction with radiations [42], tailored GNPs for use in the detection and treatment of cancer are being developed at an increasing rate. GNPs in particular have received a lot of attention for cancer research in the past years because of their straightforward production, surface changes, considerably enhanced and variable optical properties, and exceptional biocompatibility for clinical methods [43].

Executing therapeutic NPs holds the promise of greatly enhancing tumor treatments and reducing detrimental effects as a growing concept that allows for rapid prediction and treatment [12]. Due to their unique characteristics, such as their capacity to interact with various medications, retention in tumor tissues, light absorption in IR light, and exposure to radiation, GNPs are utilized in the treatment of cancer. In order to destroy tumor cells or tissues that may have the potential to be used in clinical settings, numerous types of cancer treatment research by GNPs have been applied photothermally [44]. The structure of bacterial cells and tumor tissues can be destroyed by GNPs when the cancer cells are exposed to concentrated laser light of the right wavelength [45].

Gold nanostructures need to be biocompatible and show tumor cells to be superior to healthy cells for GNPs to be used effectively in the treatment of cancer [46]. Gold-based NPs can be created to specifically target tumor tissues during active tumor therapy and minimize adverse effects on healthy cells. In order to increase cancer cell targeting and cellular uptake for efficient cancer treatment, numerous strategies are used. These methods are often divided into two classes: active target methods and passive target methods.

Due to the Enhanced Permeability Retention (EPR) mechanism, the passive target technique relies on GNPs in the cancer area growing passively [47]. Trials have used a variety of ligand molecules, including proteins, antibodies, nucleic acids, hormones, and tiny molecules, to increase the killing of cancer cells by specific chemical processes. Typically, these methods rely on the interaction between GNPs ligand and associated cancer tissue components [46].

Different surface plasmon resonances can be seen when GNPs are positioned close to one another. Therefore, when combined with anti-epidermal growth factor receptor antibodies as a biomarker agent, they can distinguish between cancerous and normal cells [47]. In the previous five years, it has been predicted that 24.6 million people have survived and received treatment for cancer. Radiotherapy is used to treat almost half of those who are affected by this disease each year. Radiotherapy techniques still face the challenging task of administering a therapeutic dose of radiation to destroy the cancer cells while preserving the healthy cells. Over twenty years ago, when iodine salt was being used to sensitize cell cultures, the concept of applying high material to enhance dosage form to cancer cells during radiotherapy was developed.

Chemotherapy

Because of the drug's lack of specificity and deadly effects on nearby non-tumor cells, developing and successfully treating tumors is a difficult task. A targeted treatment depends on precisely delivering an active substance to the target by utilizing various affinity reagents, such as those mediated by ligand-receptor, lecithin-carbohydrate, or antigen-antibody recognition [49].

The relatively haphazard introduction of chemotherapeutic drugs into healthy and malignant cells in tissue and organ systems makes conservative chemotherapy both influential and well-known for its severe negative effects [50]. With the introduction of nano-sized medications in recent years, which offer a considerable association with chemotherapy as a unique drug, major advancement has been established.

Radiotherapy

Around 50% of all cancers that are infected can be cured with radiotherapy, which is the main treatment. The effectiveness of the treatment depends on the drug dose that is deposited into cancer cells. This is typically done by bombarding cancer cells with high-energy X-rays, gamma rays, or high-energy ions, which may be enough to irradiate the tumor cells' cell membranes and ultimately lead to their demise [45]. Additionally, recent chemotherapeutics in the present day are characterized by the incorporation of NPs in nanosize drugs, which have successfully enhanced therapeutic action. The dosage enhancement factor (DEF) controls the role played by GNPs in the growth of chemotherapeutic efficacy. The DEF of GNPs is well-defined as "the ratio of the chemotherapeutic drug intake by cancer cells when GNPs are available to the fraction of drug intake by the cancer cells when GNPs are not available."It can change depending on the location of GNPs inside infected cells as well as their number and efficacy. Gold nanoparticles (GNPs) have a number of benefits, including cheap manufacturing, good biocompatibility, a wide range of sizes, and easy functionalization through the attachment of ligands needed to target cancer cells and their organelles or longer blood circulation times [51].

Hyperthermia

It has just been revealed as a cutting-edge approach to treating tumor cells and has a great deal of potential to combat this illness. It can be described as a treatment approach in which infected cells are subjected to greater temperatures, either of which kills cancer cells [52]. This increase in cancer cell temperature affects how easily blood vessels may be penetrated, improves current flow, and eventually causes oxygenation of the cancer cells [12]. In light of this, heat reduces tissue hypoxia and can be used in conjunction with radioactive agents or anti-cancer medications to enhance their cytotoxic effects on cancer. The part of a person's body where cancer is present is heated to a temperature of 40–45°C during old hyperthermia, which is a few degrees above body temperature [47]. Tools that

produce electromagnetic or ultrasonic radiations are used outside to create heat [53]. For the treatment of several types of malignancies, traditional hyperthermia is frequently used in conjunction with chemotherapy and radiation treatment methods [12]. In order to destroy tumor tissues, gold-based NPs' heat can be used as a cancer treatment.

The difference between the conventional photo-thermal treatment method [54] and hyperthermia is that the latter is a heat treatment that may occur photothermally in the vicinity of gold-based NPs, and cell temperature can rise by up to 100 degrees Celsius over body temperature [43]. It has been proposed that photo-thermal heat treatment may be more successful in treating cancer cells than healthy cells in order to counteract the negative effects of cancer treatment approaches [55]. Hyperthermia has historically been used to treat a variety of cancer types in several experimental studies, often in conjunction with radiotherapy and chemotherapy. In cancer therapy, the heat generated by GNPs is employed to halt the development of malignant cells. Traditional [52] and photo-thermal therapy differ in that photo-thermal treatment only takes place in zones directly around GNPs and that the limited temperature =-098nges can rise to a hundred degrees over physical temperature. This suggests that photothermal therapy may be able to more effectively target cancer cells while sparing healthy tissues, thereby reducing the negative effects of cancer treatments [6].

General applications of gold nanoparticles

The ideal Nano carriers for therapeutic purposes are gold nanoparticles (GNPs) because of their simplicity in production, functionalization, and biocompatibility [56]. GNPs are currently used as possible drug delivery mediators for introduction into tumor cells in cancer therapy [57]. Through ligand-receptor interaction or other non-specific mechanisms, the cells absorb colloidal gold nanoparticles of various sizes and shapes [58]. Gold nanoparticles are coupled with suitable surface ligands that solely direct them to tumor cells, as illustrated in Figure 3, in order to validate the specific killing of cancer cells.

There have been two approaches documented for tumor targeting: the first involved combining gold nanoparticles (AuNPs) with polyethylene glycol (PEG), and the second involved combining AuNPs with an antibody that binds certain biomarkers found on tumor cells. PEG increased blood retention by inhibiting the agglutination of GNPs. The buildup of AuGNPs in tumor cells as a result of the highly permeable blood arteries that are poorly differentiated around tumors, as seen in Figure 4.

By improving solubility, in vivo stability, and biodistribution, drug delivery systems (DDSs) give positive characteristics to a "free" drug. They can also alter the undesirable pharmacokinetics of some "free" medications. Additionally, heavy pharmaceutical loading on DDSs can produce a "drug reservoir," for controlled and prolonged release to maintain the drug level within the therapeutic window.

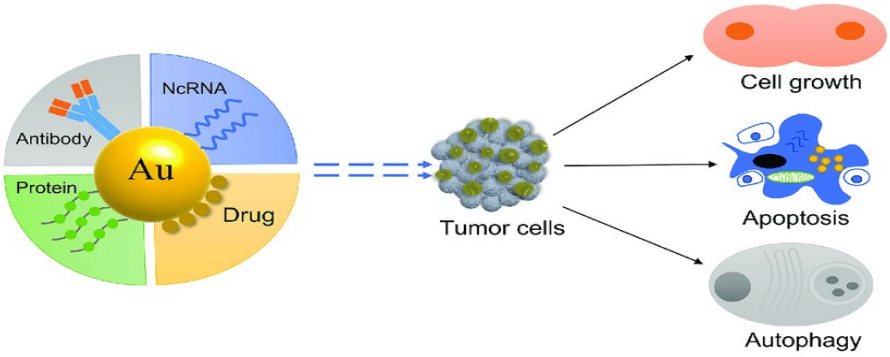

Figure 3: GNPs carriers with anticancer cells and ligands.

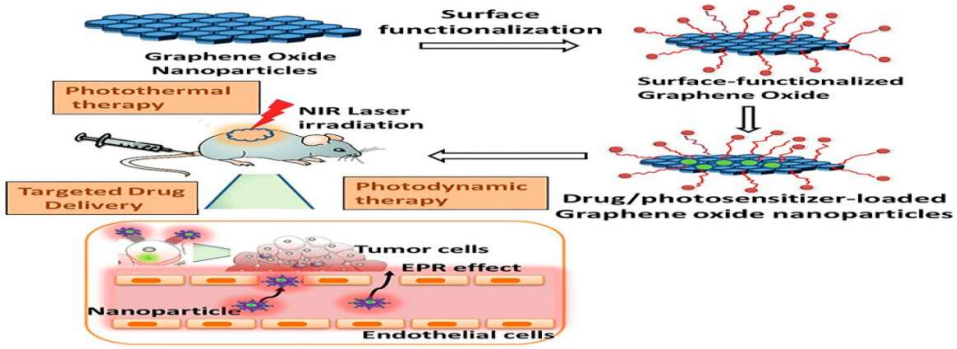

Figure 4: Accumulation of ligand-targeted gold nanoparticles conjugated with anticancer drugs in cancer cells.

Biosensor uses for gold nanoparticles

Old nanoparticles that have been functionalized with a biomolecule that has undergone thiolation have been used to create a biosensor that, after determining the complementary biomolecules, results in a change in the optical absorption of GNPs. Plasmon absorption changes when gold nanoparticles functionalized with antigen (antibody) mix and attach to the appropriate antibody (antigen).

Gold nanoparticles applications for immunosensors

Colloidal GNPs are the most often used type of nanoparticle in the lateral flows immunosensing (LFIS) method. The LFIS approach is based on immunological responses, where an antigen is identified by a specific antibody that has been labelled with different markers, such as GNPs or latex beads. LIFS can be categorized as quantitative, qualitative, or

semi-quantitative depending on the method of detection. Immunosensors can detect small analyte quantities with exceptional precision. The anodic stripping voltammetry technique and colloidal gold were used to create a novel and useful electrochemical immunoassay for immunoglobulin (IgG). A brand-new electrochemical immunoassay of the precipitation of silver on labels made of colloidal gold is displayed in Figure 5. The sensitivity of the electrochemical immunoassay is increased by the autocalytic deposition of Au+3 onto GNPs.

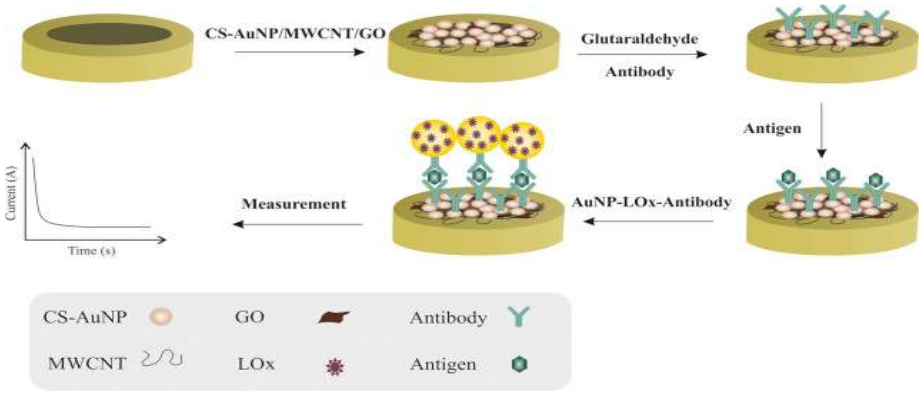

Figure 5: Gold nanoparticles for immunosensors.

Conclusion

A better potential for the treatment of cancer in numerous sections of the human body is provided by the use of gold nanoparticles (GNPs). In the medical field, GNPs are important adjuvants that reduce the toxic effects, boost the immunogenic effects, provide storage stability for medications and other treatments used in immunizations, and also have excessive potential. Additional applications for functionalized gold nanoparticles (GNPs) in medical technology include biosensors, various immune systems, experimental clinical sciences, genomics, laser therapy for the treatment of tumors and cancer cells, drug delivery, antigen and DNA scanning, imaging, and cancer cell control. The primary goal of this article is to focus on the problems that have previously been encountered during cancer therapy, such as targeted therapy and the use of chemotherapy and radiotherapy together. Thus, by releasing chemotherapeutics under controlled conditions, systems based on gold nanoparticles (GNP) are very helpful in further improving chemotherapy.

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