Gold and Silver Nanoparticles: Synthesis Methods, Characterization Routes and Applications towards Drugs

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Abstract

Nanoparticles are widely used in the biotechnology and biomedical field. Their large surface area, remarkable physical properties, enhanced permeability, and retention effect make them as promising candidates in biomedical applications such as diagnosis and therapy. The gold and silver nanoparticles proved to be the safest for drug applications. The gold and silver nanoparticles are considered very important and interesting for several applications. This review provides a summary of Au and Ag nanoparticles synthesis, characterization, and applications. The review will focus on the use of nanoparticles in drug delivery and in determining and sensing of drugs in pharmaceuticals.

Keywords: Synthesis; Gold nanoparticles; Silver nanoparticles; Applications

Introduction

The nano is a Greek word, which means small in size. It is used as the prefix for the billionth from the range 9 to 10. Particles which have two or more dimensions in the size range as 1 to 100 NM are defined as nanoparticles (ASTM International) [1]. Nanoparticles have unique chemical and physical properties as compared to their solid bulk materials because of their high surface area and electronic properties. Furthermore, these particles have been utilized in many applications, for example, electrochemistry, photochemistry, and biomedicine [2]. Nanoparticles have many functional platforms that can be utilized for imaging and therapeutic functions. These platforms can be prepared from various inorganic and organic materials, but the inorganic platforms are very important for simultaneous therapy and diagnosis because of their easy modification, high drug loading capacity and stability [3]. Nanoparticles can be used in drug delivery and in the determination of drugs in pharmaceuticals [4].

Gold nanoparticles are widely used in biotechnology and biomedical field because of their large surface area, and high electron conductivity [5]. The modification of the nanometers is conducted to enhance the interaction of these nanoparticles with biological cells [6]. Enhanced permeability and retention are the unique property of nanoparticles to accumulate and interact with the tumor cells. Drug delivery systems depend on nanoparticles, which is used in targeting malignant brain tumors where the conventional therapy is not as much effective [7]. The gold nanoparticles proved to be the safest and much less toxic agents for drug delivery [8]. Nanoparticles such as dendrimers, quantum dots, polymer gels, and gold nanoparticles have more properties and widely used in some application such as drug delivery systems and imaging [9]. Inorganic nanoparticles are widely used as a contrast agent in some application, especially molecular imaging such as computed tomography, positron emission tomography, magnetic resonance imaging, optical imaging, and ultrasound [10].

Gold nanoparticles are synthesized via different techniques [11]. One of the methods to synthesize Au/NPs is laser ablation by Ref. [12]. In addition, there are some applications of gold nanoparticles in electrochemistry involving the determination of Pharmaceutical compounds. It is commonly used in the electrochemical methods because of its ease of fabrication, better sensitivity determination and modification surface. AuNPs are proper for some surface immobilization, acting as conducting materials and enhancing the electron transfer between the surface of gold nanoparticles and the target analyte. Many procedures had been constructed to develop the immune sensor by using modified carbon paste electrode with gold nanoparticles [13]. Colloidal gold, produced by different methods, is used in the medical application. Faraday discovered the formation of gold, which has a deep red color as a liquid solution by chloroaurate reduction (AuCl₄⁻) with phosphorus in water mixture. Gold nanoparticles have many applications, such as catalysis, optical molecular sensing, cancer therapeutics, and construction blocks in nanotechnology [14].

The applicability of gold nanoparticles in drug delivery systems [15] is due to have some of the properties to make it good vehicle property for drug delivery. Fabrication of gold nanoparticles can perform to have a different size from 1 nm to 150 nm [16]. Their structural design enables the coating of the surfaces with various targeting agents. In addition, the important properties are non-toxic and biocompatible [17].

The gold nanoparticles have good physical, chemical and optical properties are presented in Ref. [18]. The individual physical, chemical, and photo properties of gold nanoparticles can be innovative ways to control the transport pharmaceutical compounds and control [19].

The colloidal gold is prepared by citrate reduction method [15,16,20]. Synthetic gold nanoparticles of different structure [21] involving gold nanorods [22-24], silica - gold nanoshells [25] and hollow gold NPs [26]. Noble metal nanoparticles distinguish from other nanoplatforms like semiconductor quantum dots, magnetic nanoparticles and polymeric nanoparticle by their single surface plasmon resonance (SPR), which has a small particle size, enhances all the radiative and inelastic properties of the nanoparticles [27].

The silver nanoparticle has many applications due to the large degree of commercialization. Silver (Ag) is an attractive material for...
its distinctive properties, such as good conductivity, chemical stability, catalytic activity, and antimicrobial activity [28]. Ag nanoparticles are used in antimicrobial applications since the antimicrobial effect of Ag ions is well known [29].

Ag NP applications include the medical field as well as in water and air filtration [30]. Furthermore, silver nanoparticles have individual plasmon optical spectra properties which allow being silver nanoparticles used in biosensing application. Table 1 summarizes some advantages and disadvantages of silver and gold nanoparticles.

The most important use of Ag/NPs includes the treatment of diseases or targeting of cells, such as interacting with the HIV-1 virus and preventing its ability to bind host cells in vitro [31]. Hybrid materials of Ag nanoparticles with amphiphilic hyperbranched macromolecules are synthesized for use in surface coatings because of its antibacterial activity [32]. The surfaces coated with Ag nanoparticles embedded paint based on vegetable oil showed excellent antimicrobial properties [33]. The water-related diseases like diarrhea and dehydration can be reduced by improving the microbial quality of the drinking water. The bactericidal activity can be reduced by the use of the Ag deposited carbon filters [34]. Bio-aerosols are the airborne particles which cause chronic diseases and developed in the ventilating, heating, and conditioning system in a humid atmosphere. The use of the Ag-coated activated carbon filter effectively removes bio-aerosols [35]. There are several commercial products for wound treatment that contain Ag as an antimicrobial agent. Nano-crystalline Ag in wound dressings is used to treat ulcers, and Ag sulfadiazine is used in pastes or creams for treating burn wounds [36].

Gold and silver nanoparticles have been commonly used in different pharmacy applications and drug delivery systems due to their inert nature, stability, high disparity, non-cytotoxicity, and biocompatibility. This review highlights the synthesis and applications of gold and silver nanoparticles in the field of pharmacy and drug delivery.

Properties of Gold and Silver Nanoparticles

Gold nanoparticles

The gold nanoparticles properties are the wine-red solution. The interactions of gold nanoparticles play an important role in their properties [37-39]. There are different sizes of gold nanoparticles start from 1 nm to 8 μM, and various shapes; for example, spherical ring, sub-octahedral, icosahedral tetrahedral, decahedral, octahedral, and nanorods (Figure 1).

Gold nanoparticles have been commonly utilized in the radiation medicine field as a radiant enhancer [40] and improvement in the therapy of radiation because the ability in drug delivery. Furthermore, Au/NPs have different uses or applications in nanotechnology as a platform for labeling of proteins and biomolecular detection.

The Au/NPs are non-toxic particles with large surface area and can be modified with other molecules, and used in biomedical fields [41]. The significance of Au/NPs in biochemistry field is due to the compatibility, and optical properties. Nanoparticles are good therapeutic agents due to their ease transport in the diseased cell and carrier-loading drug [42].

Gold nanorods are widely used in the vivo cell imaging because of resonance absorption plasmon and scatter of light in IR [43]. In addition, colloidal Au/NPs have the very small size to introduce in the tissues and cells of biological molecules such as proteins and DNA [44]. Because of their electronic properties, Au/NPs have been commonly utilized in analytical methods and used as an electrode sensor of different samples [6].

Silver nanoparticles

The potential of Ag/NPs has been widely utilized in nanomedicine, drug delivery, cosmetics, electronic application, and environmental
protection [45]. Silver nanoparticles own novel biological, chemical, and physical characteristics as compared to their solid silver bulk form [46]. Ag/NPs have special chemical and physical properties, such as surface enhanced Raman scattering and optical behavior, electrical conductivity, high thermal, chemical stability, non-linear, and catalytic activity [47]. These properties of Ag-NPs obtained in electronics, and for medical application [48]. Ag/NPs are commonly used in the antimicrobial field to treat microbes such as fungi, virus, and bacteria [49]. Due to their proven antimicrobial properties, Ag/NPs are widely used in the daily used commercial products; Ag/NPs are used in different applications, such as colloidal coating, and in paints, or in a solid material such as polymer scaffolds. In addition, Ag/NPs used in textile industry, where Ag/NPs are utilized in the filtration membranes of water due to the slow release rate of the membrane to be utilized as a protective bulkhead against different bacteria and other microbes present in the water [50].

Synthesis of Gold and Silver Nanoparticles

Different methods have been used to synthesize gold and silver nanoparticles [51]. The techniques used for the preparation of nanoparticles involved biological, physical, and chemical methods (Figure 2).

Chemical methods

**Gold nanoparticles:** Chemical technique was suggested by Gimenez et al. to prepare Au/NPs by the reduction process of the HAuCl₄ through a solution of thiolated chitosan [52]. The method of thermal citrate reduction used in the preparation of Au/NPs via Raman spectroscopy (SERS) by using inositol hexakisphosphate (IP6) to reduce HAuCl₄ [53]. In addition, the preparation of Au/NPs is by the trisodium citrate, and hydrogen tetrachlorocuprate (III) tetrahydrate (chloroauric acid) [54].

Au/NPs can be grown in encapsulated immersed in polyethylene glycol dendrimers and reduced by formaldehyde under near infra-red [55]. Gold nanoparticles are prepared by utilizing peptide-biphenyl hybrids (PBHs) as a stabilizer for gold, and in this method the size range 1.8 to 3.7 nm was reported [56]. The dendrimers/Au nanoparticles can be prepared by the reduction of a solution of HAuCl₄ and sodium borohydride [57]. The synthesis Au/NPs with size less than 10 nm can be by two various thiol involved ethylene glycol and dodecanethiol [58].

**Silver nanoparticle preparation:** The chemical methods are important to synthesize of Ag-NPs because of the simplicity of preparation in aqueous solution [59]. Monodisperse silver nanocubes were prepared by polyol process, by using a polyvinylpyrrolidone (PVP) polymer with Ag (NO₃) in the presence of ethylene glycol as reducing agent [60]. Furthermore, the shape and size of the nanotubes were based on the molar ratio of Ag (NO₃) and PVP. In this method, the particle size of Ag/NPs with 20 nm was prepared [61]. On the other hand, monodispersed Ag-NPs were prepared by using Ag NO₃, oleylamine, and liquid paraffin. Oleylamine-paraffin was utilized to control temperature and liquid paraffin was utilized in avoiding the solvents [62]. The preparation of Ag-NPs by the chemical method is based on three factors (a) stabilizing agent (b) reducing agents, and (c) Ag precursor. However, the synthesis process and shape of Ag-NPs depend on the Ag nucleus with various sizes and monodispersity which can be obtained by controlling the nucleation of Ag. This is based on factors like a precursor, pH, temperature, and reducing agents. Ag/NPs can be synthesized by utilizing Ag NO₃ as a precursor; and sodium borohydride and trisodium citrate as reducing and stabilizing agents.

![Figure 2: Different methods for synthesis of nanoparticles.](image-url)
Advantages of silver and gold Nanoparticles | Disadvantages of Nanoparticles
---|---
1 Possibility of high scale production. | 1 Less drug loading capacity.
2 Long stability [59]. | 2 Dispersion included the amount of water.
3 Controlled of active drug can be achieved. | 3 The less capacity to load hydrophilic drugs.
4 Avoided of Organic solvents. | 
5 Lyophilized [40]. | 
6 Freeze dried to form a powder formulation. | 

Table 1: Some advantages and disadvantages of silver and gold nanoparticles.

The particle size of Ag/NPs was recorded in the range from 5 nm to 100 nm and was controlled by optimizing the experimental parameters [63].

The chemical reduction approach was common for the synthesis of Ag/NPs by using organic and inorganic reducing agents. Also, various reducing agents, for example, sodium citrate, ascorbate, sodium borohydride (NaBH₄), N, N- dimethylformamide (DMF) and poly(ethylene glycol)- block copolymers elemental hydrogen, polyol process, and Tollens reagent is utilized for reducing Ag⁺ in non-aqueous or aqueous solutions. Silver ions are reduced by reducing agents to form silver (Ag⁺). These clusters lead to the formation of colloidal silver particles [64].

Physical methods

Gold nanoparticles preparation: The γ-irradiation technique is one approach for the synthesis of Au/NPs with uniform size from the range 5-40 nm and high purity, using polysaccharide alginate as stabilizer [65]. The technique of microwave irradiation was used to prepare Au/NPs by reducing agents such as citric acid and a binding agent such as cetyltrimethylammonium bromide (CTAB) [66]. Furthermore, Au/NPs are prepared by using heat or photochemical reduction, and reduction of HAuCl₄ by citrate, tartrate, and malate [66]. A common method of photochemical reduction has been recorded for the synthesis of gold-polyethylene glycol nanoparticles by polymerization reactions with size 10-50 nm. Furthermore, in this approach, gold salt is reduced by radical formation coated with polyethylene glycol diacrylate by with size 10-50 nm. Furthermore, in this approach, HAuCl₄ was used as a precursor and reduced by utilizing citrates fruit juice extracts (Citrus limon, Citrus reticulate and Citrus sinensis) [74]. The edible mushroom was also used for the preparation of Au/NPs by light power [75].

Silver nanoparticles: Using classical methods for the synthesis of Ag/NPs requires some parameters such as (a) reducing agent, (b) Ag precursors, and (c) stabilize agent (PVP) to prevent agglomeration of Ag/NPs. However, in biological or green methods, biomolecules replaced the traditional stabilizing and reducing agents. In the biological technique, Ag/NPs are prepared using green plants (such as algae, yeast, fungi, and bacteria) as stabilizing and reducing agents [76]. Shewanella one Denis reducing agent (a metal reducing agent) was utilized for the biosynthesis of Ag/NPs. The reported Ag/NPs size was less than 15 nm, with a spherical shape, and large surface area [77]. In another reported method, Trichoderma ride fungus was utilized for the green preparation of Ag/NPs from Ag (NO₃) as precursor [78]. The biopreparation of Ag/NPs with size less than 50 nm. However, the stability of Ag/NPs with size 20 nm was obtained by using the bacteria (Bacillus sp.). The green-synthesized of Ag/NPs were collected from the periplasmic region (a space between outer and inner membrane) of the bacterial cell, and phyllanthin extract at room temperature [79]. Subbaiah reported that Ag/NPs can also be prepared from Cadaba Fruticosa leaves by utilizing Ag (NO₃) as a precursor. The biological preparation of nanoparticles was very powerful against microbes [80].

Characterization of Silver and Gold Nanoparticles

Characterization of nanoparticles is significant to evaluate the nature of nanoparticles. The characterization of nanoparticles can be performed by using transmission electron microscopy, scanning microscopy (TEM, SEM), UV–Vis spectroscopy, X-ray photoelectron spectroscopy (XPS), dynamic light scattering (DLS) atomic force microscopy (AFM), powder X-ray diffractometry (XRD), and Fourier transform infrared spectroscopy (FTIR) [81].

These techniques are used for determining various properties such as the size, geometry, shape, crystallinity, and surface area. For example, the morphology shape and particle size of nanoparticles could be specified by TEM, AFM, and SEM. Particle height and volume can be measured in three-dimensional images by AFM. Moreover, determination of particle size distribution can be by dynamic light scattering. Furthermore, the determination of crystallinity is performed by X-ray diffraction, while UV–Vis spectroscopy technique is used to confirm the formation by showing the plasmon resonance.

Transmission electron spectroscopy (TEM)

In the TEM technique, a few prepared NPs were put on the carbon-coated copper grids. The micrographs of TEM for a drop of NPs are taken by utilizing the TEM instrument operated at an accelerating voltage of for example 200 kv. TEM grid is dry. A beam of photons is transmitted through an Ultra-thin specimen, and interacting with the specimen as it passes through. When the electrons transmitted through the specimen, an image is formed from the interaction. The magnification and focused on the image onto an imaging device [82].
TEM shows the size of gold nanoparticles with a different range from and illustrates the morphology image of gold nanoparticles, spherical shape, surface area, and the diameter can be indicated by this technique. TEM of silver nanoparticles can provide the morphology and the distribution of particle size for a profile of the Ag/NPs.

**Scanning electron microscope (SEM)**

This technique is used to study the size and morphology shape of the nanoparticles. A small sample was pipetted out and loaded on a stub provided for SEM analysis. The stub is made of copper, in the shape of a small cylinder about the size of 1 mm did one side of the stub was stuck with double sided carbon material. After putting the sample on the carbon material, the stub is fixed to a holder. The holder accommodates about 7 samples [83].

**Raman spectroscopy instrumental**

The Raman technique has been explored using various materials such as gold, silver, and copper metals [84]. Raman enhancement on spheres of gold and silver with magnitude orders and have been confirmed in experiments [85]. The effect of gold and silver nanoparticle size in colloids [86] and core shells [87] on the surface plasmon resonance and SERS enhancement have also been recorded. It follows from the experiments and theoretical models [88] that the maximum SERS enhancements are seen when the surface plasmon resonance wavelength is equal to \( \lambda_{p} = (\lambda_{c} + \lambda_{RS})/2 \), where \( \lambda_{p} \), \( \lambda_{c} \), and \( \lambda_{RS} \) are the surface plasmon, excitation, and Raman wavelength respectively. Furthermore, it was predicted that using different sizes of nanoparticles influences not only the surface plasmon wavelength but also the intensity of the electromagnetic field created in between the nanoparticles leading to higher SERS enhancements [89]. Differences between various metals were also investigated, revealing that the SERS enhancement of silver exceeds that of gold, which exceeds that of copper [90].

**UV-Vis spectroscopy**

The plasmon absorbance was responsible for characteristic colors of colloidal gold and silver nanoparticles. Conduction electrons on the surface of the nanoparticles and electromagnetic radiation are absorbed by incident light due to oscillations. The absorption maximum is adjusted in the range of 0.5 and 0.7; the nanoparticle solution is diluted with distilled water. The plasmon resonance produces a peak near 400 nm with PWHM of 50 to 70 nm. The wavelength of the plasmon absorption maximum in a given solvent can be used to indicate particle size. Silver nanoparticles that produce the spectrum are (\( \lambda_{max} \) 400 nm) [91]. The absorbance spectra of gold nanoparticles are observed at ~ 520 nm since the PA solution and the HAuCl₄ do not have any absorbance at this wavelength.

**IR instruments**

Synthesized Ag/NPs were determined via utilizing Perkin Elmer Spectrum One FTIR with a spectral range between 4000-400 cm in solid KBr pellet. FTIR analysis was used for the characterization of the functional groups observed on the nanoparticles. The FTIR analysis of powder samples was prepared similarly as for powder diffraction calculations. The sample is placed in the two cells of NaCl, after this the two cells contain the sample put in the holder of KBr pellet cells and eventually the detection occurs from the program on the computer to get the signal. The transmittance signal of gold nanoparticles is shown at 430.5 wavelengths and OH signals of the solution are shown at 3422.9 wavelengths (broad signal). The transmittance signal of silver nanoparticles is shown at 400 nm of the wavelength and OH signals wavelength of the solution is shown at 3422.9 nm (broad signal).

**XRD analysis**

XRD analysis is used to evaluate of a crystallite size of the aggregate nanoparticles. The measurements can be performed by using a Philips diffractometer of ‘X’ pert company with nano chromatic Cu Kβ₁ (\( \lambda = 1.54060 \) A) radiation. The size is determined by the width of XRD peaks using Scherrer’s formula, \( D = 0.86\lambda/\beta \cos \theta \). The nanoparticles size and structure were obtained and confirmed by the XRD patterns of the products taken with a small amount of the sample. Furthermore, the three diffraction peaks were indicated by the XRD pattern in which agreed with (111), (200) and (220) diffractions of face-centered cubic silver. The metallic silver illustrates that high purity of FCC structure with all parameters a=4.065. Similarly, the XRD patterns of silver nanoparticles synthesized using n-butyl alcohol solvent shows a characteristic peak at 2θ=38.5, marked with (111). It confirms the hypothesis of mono crystalline. The sharpening of peak clearly indicates that the particles are in the nano range. The particle size was also found the value is higher than the ethylene glycol solvent. Hence, the particle size of silver nanoparticles is 9.99 nm and 42 nm for ethylene glycol and n-butyl alcohol respectively. The data are compared with the reported pure silver nitrate sample [92].

**Application of Gold and Silver Nanoparticles**

Figure 3 illustrates the various applications of nanoparticles in the pharmaceutical field. The wide applicability of the silver and gold nanoparticles is due to the novel properties of the nanoparticle, which help with applications excellent catalytic, good biocompatibility, large surface area, and conductivity. The bio sensing applications are widely used when the nanoparticles combined with biomolecules and used in combination of Au/NPs and AuNPs/MPA (mercaptopropionic acid) used in the fabrication of biosensors which shows a wide linear range between 0.25 mM and 1.25 mM glucose concentration having detection limit of 0.025 mM [93].

On the other hand, Ag/NPs have been widely used and known as an antimicrobial agent in the United States of America since 1954 [94]. Therefore, there is a more traditional approach to utilizing silver and gold by the ancient Egyptian and Romans. The oxidation state of Ag⁰ and Ag⁺¹ are more stable compared with other oxidation states and can form different complexes.

**Application in biomedical**

Nanoparticles are used as biolabels in biomedical applications [95]. Immobilization and labeled of biomolecules on nanoparticles to give...
hybrid molecules have been reported by different methods involved specific recognition, covalent coupling, physical adsorption, and electrostatic binding [96]. Gold nanoparticles are for example used in the gene therapy in vivo delivery, proteins, delivery of nucleic acids, and targeting [97]. Figure 4 illustrates the biomedical applications of the gold nanoparticles.

**Gold nanoparticle application in drug delivery**

The nanoparticles flow in endocytosis and are diffused through the lipid bilayer of the cell membrane. Nanoparticles conjugated with antibodies against exclusive cancer cell surface receptors are used to specifically bind with cancerous cells. The functionalized nanoparticles are used for targeted entry into cells. Phthalocyanine-stabilized gold nanoparticles have been shown to be a potential delivery vehicle for photodynamic therapy [98]. Functional nanoparticles of gold nanoparticles with a size of 20 nm were conjugated to different cellular targeting peptides to penetrate the biological membrane and target the nucleus. Different nanoparticles have also applied as targeted drug-delivery and biomarkers agents for diagnosis and medical treatment of cancer. Gold nanoparticles functionalized with targeted specific biomolecules can effectively destroy cancer cells or bacteria (Figure 5) [99]. Large surface to volume ratio of gold nanoparticles offers a large number of drug molecules being carried by the gold nanoparticles [100]. The functionalized nanoparticles used in drug delivery was demonstrated in Figure 6.

**Silver nanoparticle application in drug analysis**

Silver nanoparticles are commonly used due to their electrical conductivity, wide antimicrobial activity against various microorganisms and localized surface plasmon resonance effect [101,102]. The Ag/NPs have an important role in many applications such as surface-enhanced Raman scattering, catalyst, sensors, biomedical and antimicrobial applications. Insertion of Ag/NPs onto supports is important for further exploration of Ag/NPs properties. For example, Wei et al. reported that the introduction of Ag/NPs into GO sheets indicate that the antibacterial performance of Ag/GO nanohybrids were enhanced compared with Ag-NPs alone. The Ag/GO hybrids show the non-toxic effect on rat skin [103]. Other reports [104] showed excellent antimicrobial activity for Ag/GO nanohybrids. Figure 7 illustrates the synthesis of silver nanoparticles and used in drug analysis.

**Conclusion**

Gold and silver nanoparticles are prepared by various methods and used in different fields including drug delivery, sensing, and detection. The wide applicability is due to their extremely chemical and physical, high surface area, tunable optical, stability, properties small size, and non-cytotoxicity. Functionalized silver and gold nanoparticles with different biomolecules such as proteins, DNA, amino acids, and carboxylic acids have been used in cancer therapy and provide excellent drug delivery system. Targeted gold nanoparticles delivery interacts with the cancerous cell. Side effects of conventional drugs have been minimized by conjugation with gold nanoparticles. Ag/NPs have proven worthy in inhibiting the microbial proliferation and microbial infection. Furthermore, Ag/NPs have added a new dimension in the field of medicine concerning wound dressing and artificial implantation and in preventing contamination caused by microbes. Apart from that, Ag/NPs play a pivotal role and are considered as important ingredients in the preparation of commercially used products in industries.

![Figure 4: The potential application of Gold nanoparticles in the biomedical field.](image_url)
Figure 5: Functionalized GNP’s (f-GNP) for drug delivery.

Figure 6: Applicability of gold nanoparticle in different fields including targeting, separation, drug delivery, sensing, and detection.
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