Synthesis of Long-Term Stable Gold Nanoparticles Benefiting from Red Raspberry (Rubus idaeus), Strawberry (Fragaria ananassa), and Blackberry (Rubus fruticosus) Extracts—Gold Ion Complexation and Investigation of Reaction Conditions

Ayse Demirbas,† Kasim Büyükbeyzirici,‡ Cagla Celik,‡ Emin Kislakci,‡ Zehra Karaagac,‡ Ersen Gokturk,§ Ahmet Kati,∥ Behzat Cimen,⊥ Vedat Yilmaz,*‡ and Ismail Ocsoy*‡

†Recep Tayyip Erdogan University, Faculty of Fisheries and Aquatic Sciences, 53100 Rize, Turkey
‡Department of Analytical Chemistry, Faculty of Pharmacy, and ‡Department of Biochemistry, Faculty of Pharmacy, Erciyes University, 38039 Kayseri, Turkey
§Department of Chemistry, Hatay Mustafa Kemal University, Tayfur Sokmen Campus, Alahan, Antalya City, 31001 Hatay, Turkey
∥Biotechnology Department, Institution of Health Science, University of Health Science, 34001 Istanbul, Turkey

Supporting Information

ABSTRACT: We report synthesis of monodispersed, stable, and colloidal gold nanoparticles (Au NPs) using anthocyanin-riched red raspberry (Rubus idaeus), strawberry (Fragaria ananassa), and blackberry (Rubus fruticosus) extracts as functions of concentration of HAuCl4·3H2O and berries extract, reaction time, and reaction pH values (pHs) and demonstrate their unique stability in highly concentrated salt (sodium chloride, NaCl) solutions. The catecholamine group of anthocyanin molecules give preferential coordination reaction with gold ions (Au3+) for creating anthocyanin−Au3+ complexes, which may lead to initiation of nucleation for seed formation, and then, oxidation of catecholamine results in a flow of electrons from anthocyanins to Au seeds for anisotropic growth. Finally, the surface of the Au NPs is saturated with anthocyanins, and formation of monodispersed and stable Au NPs with narrow size distribution is completed. We also report the effects of some experimental parameters including concentrations of Au3+ ions and barrier extracts, reaction time, and pHs on formation of the Au NPs with rational explanations. The long-term colloidal stability of the Au NPs in the 400 mM NaCl solution was comparatively studied with commercial Au NPs (citrate capped). As results show that anthocyanin-riched berry extracts directed Au NPs we proposed here can be considered as promising and safe tools for biomedical applications owing to their highly much colloidal dispersibility and salt tolerance properties.

INTRODUCTION

Although synthesis of uniform and monodispersed nanoparticles (NPs) with unique intrinsic properties, including optical, magnetic, and luminescence, is accomplished in organic solvents and surfactants consisting of a long hydrophobic hydrocarbon chain at high temperature. In terms of bioanalytical and biomedical application aspects, colloidal stability of NPs in the aqueous solutions and their toxicities are the critical issues to be solved. It is worthy to mention that, when hydrophobic NPs are directly applied to living organisms, they are prone to rapid agglomeration owing to insolvency in aqueous environment, which causes serious congestion in blood vessels and may eventually lead to death. Therefore, it is necessary to produce water-soluble NPs with low toxicity and high colloidal stability.

Until now, various biomolecules including protein, enzyme, and DNA have been used as reducing and/or stabilizing agents to produce colloidal and biocompatible NPs for using them in...
biomedicine. For instance, while Kelley and co-workers developed a single designer ligand chimeric DNA-directed colloidal and functional semiconductor nanocrystals for targeted biological imaging, a similar strategy was utilized by Tan and co-workers using double stranded DNA to synthesize metallic silver (Ag), gold (Au), and copper (Cu) NP-decorated graphene oxide nanocomposites as novel and effective antimicrobial agents.\(^7\)\(^-\)\(^{10}\) In addition to that, protein, folic acids, peptides, and enzymes acted as functional ligands for production of quantum dots used as biosensing and imaging tools.\(^11\) However, major drawbacks of using these biomolecules are their high cost, risk of easy contamination, easy degradation, and the need for special storage condition. To address these issues, plant extracts are considered as alternative reducing and stabilizing agents for biosynthesis of metal and metal oxide NPs.

Up to date, different types of plant extracts have been widely utilized for formation of a variety of NPs because they are quite cost-effective or even free, greatly stable against harsh experimental conditions,\(^12\)\(^-\)\(^{23}\) easily prepared and they provide large scale production of NPs. Plant extract-based NP synthesis was developed for the first time by Shankar and co-workers using the lemongrass plant extracts for formation of gold (Au) nanoparticles.\(^24\) The polyphenols, flavonoids, sugars, and enzymes found in plant extracts play a crucial role for the reduction of metal ions and formation of NPs. Among all metallic and metal oxide NPs, Au is apparently the most popular and used NP in various scientific fields owing to unique optical, electronic, and chemical properties.\(^25\)\(^-\)\(^{29}\) The intrinsic localized surface plasmon resonance (LSPR) property of Au NPs enabled us to efficiently use them in biosensing, bioimaging, delivery vehicle, and disease ther-

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**Scheme 1. Proposed Mechanism for Au NP Formation Containing Three Following Steps: (1) Nucleation for Formation of Seeds; (2) Growth of Seeds; and (3) Formation of Au NPs**

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**Figure 1. Characterization of Au NPs.** (A) UV−vis spectra of Au NPs. Inset: photographs of Au NP solutions using (i) S. berry, (ii) R. berry, and (iii) B. berry. TEM images of Au NPs formed using 5% w/w of (B) S. berry, (C) R. berry, and (D) B. berry.
coordinated with Au3+ ions through the catecholamine groups. Basically, anthocyanin molecules acted as chelating agents, resulting in the formation of Au NPs, as shown in Scheme 1. Au3+, the anthocyanin molecules also functioned as stabilizing agents for the Au NP synthesis called "Turkevich method" used trisodium citrate as reducing and stabilizing agents at the boiling point, and the Au NPs were produced approximately in 1 h. In this protocol, not only trisodium citrate but also the high temperature acts as a driving force for thermal reduction of Au3+ ions as well. Herein, we report a systematic study on synthesis of colloidal and stable Au NPs using anthocyanin-riched raspberry, strawberry, and blackberry extracts at room temperature (RT) in roughly 20 min. We investigated formation of Au NPs as a function of the concentration of Au3+ ions, barrier extract, reaction time, and pHs. The salt tolerances of the anthocyanin-directed Au NPs and citrate capped Au NPs were comparatively studied.

**RESULTS AND DISCUSSION**

**Synthesis of Anthocyanin-Directed Au NP.** The anthocyanins, water-soluble, natural, and phenolic pigments, predominantly found in many colorful plants, especially in raspberries, strawberries, and blackberry are responsible for the coloring of these fruits. In these fruits, the cores of anthocyanins can be varied to pelargonidin-3-glucoside, cyanidin 3-glucoside types and anthocyanins can be varied to pelargonidin-3-rutinoside, and cyanidin 3-glucoside types and all of which give complexes with various metal ions.

In this study, we offer that the anthocyanins in various forms preferentially made stable complexes with Au3+ ions and resulted in the formation of Au NPs, as shown in Scheme 1. Basically, anthocyanin molecules acted as chelating agents coordinated with Au3+ ions through the catecholamine groups and gave stable anthocyanin–Au3+–anthocyanin complexes. During the incubation of the complexes under stirring, the catecholamine groups were oxidized to form quinone derivatives and the flow of electrons was orientated from anthocyanin to Au3+ for their reduction. After reduction of Au3+, the anthocyanin molecules also functioned as stabilizing agents for preparation of stable zero-valent Au NPs. The major content of berries such as anthocyanins and the total phenolic compounds were determined and given in Supporting Information (Figure S1).

Characteristic absorbance peaks of the Au NPs were monitored with UV–vis spectrophotometry owing to their strong LSPR property, Figure 1A, which exhibited that, while strawberry (S. berry) and raspberry (R. berry) extract-directed Au NPs gave sharp absorbance peaks around 521 nm shown with blue and gray lines, respectively, Au NPs formed using blackberry (B. berry) exhibited a broad peak at ~532 nm (orange line). The color of Au NP solutions using extracts of R. berry (i), S. berry (ii), and B. berry (iii) becomes ruby red (as photographs shown inset of Figure 1A), which can be a complementary indication of Au NP formation. The transmission electron microscopy (TEM) images of Au NPs in Figure 1B (S. berry), 1C (R. berry), and 1D (B. berry) show that all Au NPs are quite uniform, monodispersed, and spherical in shape with the size of 18 ± 3 nm. We claim that high concentration anthocyanins in the B. berry extract may cause some aggregative growth during the formation of Au NP, which is consistent with its slightly broad absorbance peak (orange line in Figure 1A) and the aggregated Au NP image (Figure 1D).

It is worthy to mention that the concentration of Au3+ as the monomer, must reach a supersaturation point to exceed the Gibbs free energy barrier for initiation of nucleation. Thus, the determination of the energy barrier and the critical radius of the nucleus are necessary and can vary on types of metal ions and reducing and/or stabilizing agents used in NP synthesis. For this point, formation of the Au NPs as function of various Au3+ concentrations was evaluated. All barrier extracts were determined as 5% w/w, and a series of Au3+ concentrations (0.25, 1, 2, 5, 10, and 20 mM) were used to optimize Au3+ concentration as presented in Figure 2.

For S. berry-based synthesis, when 0.25 and 1 mM concentrations of Au3+ were used, no stable Au NP formation was observed owing to formation of unstable seeds (Figure 2A). While distinct absorbance peaks of Au NPs at ~521 nm were observed using 2 and 5 mM Au3+ ions, the Au NPs synthesized via 10 and 20 mM Au3+ displays a slight red shift appeared at ~545 nm. Similarly, the R. berry-directed Au NPs formed using 0.25 and 1 mM did showed very weak peaks, but the Au NPs synthesized with 2, 5, and 10 mM exhibited quite sharp, intense, and narrow peaks at ~521 nm. The very broad and low absorbance peak was observed with use of 20 mM Au3+ (Figure 2B). We assume that using 5% w/w R. berry may partially reduce Au3+ ions and induce formation of less stable Au NPs, which may cause rapid agglomeration of the Au NPs. Surprisingly, B. berry–directed Au NPs gave absorbance peak only with 2 mM Au3+ used; no apparent absorbance values were recorded when used with other Au3+ concentrations.

![Figure 2](image-url)
(Figure 2C). It is considered that 2 mM Au\(^{3+}\) toward the 5% w/w B. berry extract is optimum concentration for complete reduction of Au\(^{3+}\) ions and formation of Au NPs. It is a fact that complete reduction of metal ions can be achieved with suitable metal ion and reducing agent concentrations.

We demonstrated that S. berry and R. berry extracts with 1, 5, and 20% concentrations resulted in formation of the Au NPs with characteristic LSPR peaks (Figure 3A,B). However, ideal Au formation with sharp and narrow absorbance peak was not observed using the 5% B. berry extract (blue line in Figure 3C). The Au NPs with corresponding LSPR peaks were obtained using at least 10 and 20% B. berry extracts. As we claim in Figure 2 that for synthesis of monodispersed NPs, occurrence of homogeneous nucleation is necessary and only possible when a stable nucleus is formed, all of which is directly dependent on the type and concentration of the reducing agent found in barrier extracts. The anthocyanin molecules acting as both reducing and stabilizing agents are essential components in berry extracts and are found with similar amounts in S. berry and in R. berry extracts compared to B. berry (data not shown). This explanation is quite consistent with UV–vis spectra of Au NP solutions in Figure 3.

For further evolution of Au NP synthesis, formation of berrydirected Au NPs was examined as a function of the reaction time through UV–vis spectra. Figure 4 shows that, distinct characteristic LSPR peaks of Au NPs formed using berry extracts were observed at around 40 min; however, R. berry-directed Au NPs gave a sharp peak LSPR peak at around 10 min (Figure 4B). The very broad LSPR peaks of Au NPs can be an indication that formation of Au NPs was initiated but not completed in 10 min. When S. berry and B. berry extracts as shown in Figure 4A (pink line) and 4C (pink line), respectively. We propose that anthocyanin groups in the R. berry extract may rapidly and strongly react with Au\(^{3+}\) ions to form stable Au NPs compared to ones in S. berry and B. berry extracts.

The pH values of reaction solutions may influence both formation and stability of Au NPs in aqueous solutions owing to alteration of charge density on the surface of Au NPs. Although the anthocyanins found as major components in berry extracts are easily protonated to have positive charge in
acidic solution compared to polyphenols and flavonoids, the tendency of charge-density can be related to types of anthocyanin groups. UV−vis spectra demonstrated that the S. berry extract formed stable Au NPs at pH 8 (red line) and 13 (light blue line) with sharp LSPR peaks. The Au NPs formed at pH 2 (dark blue line) and pH 5 (pink line) using S. berry extracts are unstable in aqueous solutions and rapidly tend to aggregate owing to the incomplete reduction of Au3+ ions as shown in Figure 5A. In Figure 5B, Au NPs synthesized at pH 5 and above using R. berry extracts stay dispersed in the aqueous solutions, but Au NPs tend to aggregate when synthesized at very acidic solution (pH 2). Interestingly, the B. berry extract used as reducing and stabilizing agents resulted in long term stable Au NPs at all acidic and basic pH values, as presented in Figure 5C. We claim that two potential mechanisms can be documented for elucidation of stability of Au NPs based on reaction solution pHs: (1) The anthocyanins in the S. berry extract are easily positively charged at low and medium acid solutions, which may affect their binding strength on the surfaces of Au NPs and (2) the electrostatic repulsion between Au NPs can be decreased owing to the positive charge of anthocyanins, which may result in aggregation of Au NPs. If the anthocyanins are not highly protonated, they act as strong reducing and capping agents for formation of stable Au NPs and provide well dispersed Au NPs in long term, which are consistent with UV−vis spectra of Figure 5B,C.

It is worthy to mention that aggregation of NPs strictly reduces their properties and limits applications of NPs. For instance, NP aggregates may be life-threatening when used in living organisms. The salt-induced aggregation can be considered as a major problem for water-soluble NPs. In Figure 6, we systematically studied the salt tolerance of the Au NPs based upon electrostatic and capping agent stabilization. The first protocol for Au NP synthesis was introduced in 1951 by Turkevich and co-workers called “Turkevich”. In this typical method, Au NPs were produced using trisodium citrate for reduction of Au3+ and stabilization of Au NPs under the boiling point of Au3+ solution. Although it is almost the most common method for synthesis of monodispersed and uniform Au NPs in aqueous solution, Figure 6A showed that citrate-capped Au NPs have weak stability in salt solution, while the citrate-capped Au NP solutions gave a characteristic red wine color and sharp absorbance peaks at around 525 nm in between 5 and 20 mM NaCl solution. However, increasing concentration of NaCl solutions from 50 to 400 mM induced aggregation of Au NPs, which caused color change from red to purple/blue, and very broad and shifted LSPR peaks appeared at around 570 nm, as shown in Figure 6A. Surprisingly, Figure 6B posed that berry extract-directed Au NPs are quite stable even in high concentrations of NaCl solutions (from 5 to 400 mM) without Au NP aggregates. No shift in absorption maximum and no color change in berry extract-directed Au NPs were observed. It is known that salt solution can alter the charge density on the surface of metallic NPs and decrease the energy barrier between NPs, all of which may bring NPs in proximity with each other and induce aggregation. We claim that anthocyanins in berry extracts strongly bind to Au NPs as...
Capping agents and provide electrostatic stabilization even in 400 mM NaCl solution, and eventually, aggregation of Au NPs is prevented. We also provided a scanning electron microscopy (SEM) image of anthocyanins (S. berry extract)-capped Au NP to show colloidal and stable Au NPs in high concentration NaCl solution without agglomeration, as shown in Supporting Information (Figure S2). This explanation is consistent with dynamic light scattering (DLS) results of Au NPs, as shown in Figure 7.

Figure 7 demonstrates that, while the effective diameter of citrate-capped Au NPs dispersed in water was around 30 nm, their effective size increased to ~110 nm in the presence of 100 mM NaCl solution. In contrast, DLS measurements show that anthocyanins (S. berry extract)-capped Au NPs dispersed in water and 100 mM NaCl solution showed effective sizes of around 37 and 45 nm, respectively. We may conclude that anthocyanins in berry extracts effectively stabilize the Au NPs and provide unique colloidal stability by preventing them from aggregation for several months.

■ CONCLUSIONS

We produced colloidal and monodispersed Au NPs using anthocyanin-rich red raspberry (Rubus idaeus), strawberry (Fragaria ananassa), and blackberry (Rubus fruticosus) extracts used as reducing and stabilizing agents. We studied experimental parameters, such as HAuCl₄·3H₂O concentration, berry extract concentrations, reaction time, and reaction pH values (pHs), to demonstrated how they influence the formation of Au NPs. Benefiting from complexation ability of anthocyanins with gold ions (Au³⁺), the Au NPs exhibited dramatically enhanced colloidal stability in 400 mM NaCl solution compared to commercial Au NP (citrate capped) as they did not aggregate in 50 mM NaCl. We suggest that anthocyanins can be promiscuously alternative reagents to synthesize stable and uniform Au NPs at RT for 30 min without any additional reagent and stimulilike thermal reduction.

■ MATERIALS AND METHODS

Chemicals and Instrumentation. Gold(III) chloride trihydrate (HAuCl₄·3H₂O), sodium hydroxide (NaOH), hydrochloric acid (HCl), and sodium chloride (NaCl) were obtained from Sigma-Aldrich. Red raspberry (R. idaeus), strawberry (F. ananassa), and blackberry (R. fruticosus) were purchased from a local market. Deionized water (18.2 MΩ) from Millipore Co., USA, was used in all experiments. UV−vis spectrometer, SEM, DLS, and zeta potential (ZT) instruments were used for characterization of the Au NPs.

Extract Preparation. The extracts of red raspberry (R. idaeus), strawberry (F. ananassa), and blackberry (R. fruticosus) were prepared by following a modified method. Typically, freshly purchased model berries were cut into small parts and mixed with 100 mL distilled water into three different 500 mL glass beakers. Each beaker was exposed to microwave (using 900 W power) for 2 min. After that, each mixture was filtered to obtain aqueous extracts.

Preparation and Characterization of Au NPs. Various concentrations of Au³⁺ and berry extract solutions were mixed in a glass vial, and each mixture was incubated at room temperature (25 °C) under mild stirring for different time periods. The characteristic LSPR absorption peaks of the Au NPs are shown in Supporting Information (Figure S2). The major chemical contents of each berry and the SEM image of the Au NPs in NaCl solution (PDF)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02469.

The major chemical contents of each berry and the SEM image of the Au NPs in NaCl solution (PDF)

■ AUTHOR INFORMATION

Corresponding Authors
* E-mail: vedatyilmaz1980@gmail.com (V.Y.).
* E-mail: ismailocsoy@erciyes.edu.tr (I.O.).
Author Contributions
A.D. and K.B. contributed equally. The manuscript was written through contributions of all authors. A.D., K.B., C.C., E.K., B.C., and Z.K. performed experiments. I.O. and C.Y. conceived the original idea and supervised the project. I.O. and E.G. made contributions to design the project.

Notes
The authors declare no competing financial interest.

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