Green Synthesis of a Novel Silver Nanoparticle Conjugated with Thelypteris glandulosolanosa (Raqui-Raqui): Preliminary Characterization and Anticancer Activity

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Abstract: In the last decade, the green synthesis of nanoparticles has had a prominent role in scientific research for industrial and biomedical applications. In this current study, silver nitrate (AgNO₃) was reduced and stabilized with an aqueous extract of Thelypteris glandulosolanosa (Raqui-Raqui), forming silver nanoparticles (AgNPs-RR). UV-vis spectrophotometry, dynamic light scattering (DLS), and scanning transmission electron microscopy (STEM) were utilized to analyze the structures of AgNPs-RR. The results from this analysis showed a characteristic peak at 420 nm and a mean hydrodynamic size equal to 39.16 nm, while the STEM revealed a size distribution of 6.64–51.00 nm with an average diameter of 31.45 nm. Cellular cytotoxicity assays using MCF-7 (ATCC® HTB-22™, mammary gland breast), A549 (ATCC® CCL-185, lung epithelial carcinoma), and L929 (ATCC® CCL-1, subcutaneous connective tissue of Mus musculus) demonstrated over 42.70% of MCF-7, 59.24% of A549, and 8.80% of L929 cells had cell death after 48 h showing that this nanoparticle is more selective to disrupt neoplastic than non-cancerous cells and may be further developed into an effective strategy for breast and lung cancer treatment. These results demonstrate that the nanoparticle surfaces developed are complex, have lower contact angles, and have excellent scratch and wear resistance.

Keywords: Thelypteris glandulosolanosa; green synthesis; AgNPs; breast cancer; lung cancer; Raqui-Raqui

1. Introduction

Breast and lung cancers are amongst the most frequently diagnosed cancers worldwide, causing over one million deaths annually [1–6]. Conventional cancer treatment shows several limitations, including low or no specificity and low efficacy in discriminating between neoplastic and healthy cells [7]. The typical treatments most commonly prescribed for these types of cancer include chemotherapy [8–10], which is administered
to therapeutically control tumor growth and prolong patient survival [11]. However, chemotherapy of anticancer drugs often have several limitations including vascular administration and extravasation, low or no oral bioavailability [12,13], rapid elimination [14], adverse side effects [15–17], non-specific off target cytotoxicity [13,17–20], and multidrug resistance [21,22].

For approximately 50 years, natural products have provided sources of chemotherapeutic molecules in combating cancer [16,23–33]. The primary sources of these successful compounds are plants from terrestrial environments [34,35]. Among several terrestrial plants, the ferns are widely distributed in the world, mainly in India [36,37], Türkiye [38], Nepal [39], Japan [40], and Peru [41–44], with some species having been used in food or folk medicine for centuries [45]. Ferns comprise over 12,000 species spread among 250 different genera [46]. The secondary metabolites of these ferns have been reported to have antioxidant [47,48], anti-inflammatory [49,50], anticancer [49,51,52], and antimicrobial [53] activities. Among these ferns, Thelypteris torresiana contains the secondary metabolites protoapigenin [54], flavotorresin [55,56], 2′-hydroxy-2′,3′-dihydroprotoapigenone acetonide [53], 2′,6′-dimethoxy-tetrahydroprotoapigenone [54], and tetrahydroprotoapigenone [55] that have antitumoral activity. Thelypteris torresiana produces protoapigenone [57–60] that has been reported to exhibit significant antitumor activity against lung cancer cells (A549) [61], liver cancer cells (Hep G2 and Hep 3B) [58], and breast cancer cells (MCF-7 [62] and MDA-MB-231) [61] with IC$_{50}$ values ranging from 0.23 to 3.88 µM [63,64]. The novel flavone protoapigenone has been reported to decrease cancer cell viability through the induction of apoptosis [65,66]. Furthermore, it has exhibited significant anticancer activity in a nude mouse model explanted with human ovarian and prostate cancer cells [65–67].

Raqui-Raqui (Thelypteris glandulosolanosa) is a species of fern. A review of PubMed and EMBASE does not demonstrate peer-reviewed publications with biomedical applications to date. However, its similarity to Thelypteris torresiana would suggest that bioactive compounds with potential anti-tumor activity are likely possible. Other ferns that belong to the Thelypteris genus have been studied such as Thelypteris normalis that contains various allelopathic compounds such as thelypterin A and B [68], the presence of the anthelmintic and fungicide benzimidazole in Thelypteris felix-mas [69], and the content of various drimane-type sesquiterpenoids in Thelypteris hispidula (Decne.) Reed [70,71]. The Thelypteris palustris has been used for arsenic and other heavy metal uptake phytoremediation [72–75].

The potential of plant-based nanoparticles to treat different cancers is being extensively studied and well reviewed [76] and the application of silver and gold nanoparticles to treat cancers is a very active area of research investigations [76–80]. Recent studies revealed that the use of the various metallic nanoparticles in medical sciences has various applications, such as bio-imaging [81–84], bio-sensing [85–87], and drug delivery [88–90] of nutraceuticals [23,26,91–99], and pharmaceuticals [17,20,31,100], which could affect disposition [13,24,25,27–30,32,33,101–117], lymphatic transport [118], ophthalmic drug delivery [119], and toxicity [16,19,120–122]. Often, various chemical and physical methods used for the preparation and syntheses of nanoparticles involve hazardous and toxic chemicals [123], high-cost laboratory apparatus and infrastructure [124,125], as well as capabilities of varying conditions such as temperature and high pressure [126]. Recently, a new biological approach has been developed for nanoparticle synthesis, which utilizes organic material to reduce bioactive agents isolated from plants [127–129]. These biotechnologies have low cost and are environmentally safe compared to other chemical and physical processes [130].

Our research group has previously synthesized and characterized functionalized cotton fabric with silver nanoparticles and carboxymethyl chitosan (AgNPs-CMC) [131,132]. The nanocomposite obtained from the complex [Ag (NH$_3$)$_2$]$^+$ was synthesized under similar conditions and verified the formation of silver nanoparticles [131]. Our results, as characterized by Dynamic Light Scattering (DLS) for AgNO$_3$, revealed a monodisperse distribution of the nanocomposite with an average hydrodynamic size of 166.7 nm [131]. Fourier Transformation Infrared spectroscopy (FT-IR) demonstrated the inhibition of spec-
central bands at 879 and 723 cm$^{-1}$ indicating the presence of AgNPs in the nanocomposite [131]. Scanning electron microscopy (SEM) demonstrated that the silver nanoparticles were spherical in shape and between 5 and 20 nm [131]. The functionalized fabric evaluated using X-ray diffraction (XRD) analysis further confirmed the presence of silver nanoparticles [132]. Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) determined an average concentration of 13.5 mg of silver per kg of functionalized fabric [132]. IR reported that the functionalized fabric variation had a displaced peak of intensity at 1594.32 cm$^{-1}$, corresponding to carboxylate anions [132]. Similarly, Raman spectroscopy demonstrated an intense peak at 1592.84 cm$^{-1}$, which is characteristic and corresponds to the primary amino group of carboxymethyl chitosan, and a peak at 1371.5 cm$^{-1}$ corresponding to the carboxylic anions [132]. Finally, the physical and mechanical tests of tensile strength and color index were similar [132]. The functionalized fabric possessed antimicrobial and antifungal properties against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus niger* [133].

Our current study is novel as it constitutes the first study of a cost-effective, eco-friendly, and convenient and facile protocol for green synthesis of AgNPs from *Thelypteris glandulosolanosa* (Raqui-raqui) leaves extract. The green synthesis methodology has recently received significant scientific attention because of its cost-effectiveness and because it is an eco-friendly technique [134–137]. Organic synthesis using various plant extracts has been previously reported in green synthesis, increasing the stability and efficiency of these nanoparticles [138–140]. The properties and efficiency of silver nanoparticles (AgNPs) depend on their morphological characteristics such as size, shape, surface area, and the type of the plant used for the synthesis of these nanoparticles [56,141]. Silver nanoparticles (AgNPs) synthesized by the biological method using *Anthemis atropatana* and *Albizia adianthifolia* have been shown to exhibit antiproliferative effects against many cancer cells [142–145]. However, the synthesis of silver nanoparticles using the aqueous extract of *Thelypteris glandulosolanosa* has not been reported and published in the literature to the best of our knowledge and review. Therefore, this study aimed to investigate the anti-cancer activity of silver nanoparticles (AgNPs) green synthesized using the aqueous extract of the *Thelypteris glandulosolanosa* on the MCF-7 breast cancer and A549 lung cancer cell lines.

The materials and methods are presented in Section 2. Section 3 provides the outcomes and discussion. Conclusions are described in Section 4.

2. Materials and Methods

2.1. Reagents and Materials

The following reagents were used: silver nitrate (Merck Millipore, Burlington, MA, USA) and methyl thiazolyl diphenyl-tetrazolium bromide (MTT) (Merck Millipore, Burlington, MA, USA).

2.2. Equipment

UV-Visible spectrophotometer (Gold Spectrum lab 54S), dynamic light scattering (DLS, Zetasizer Nano ZS), and scanning transmission electron microscopy (JEOL 2200FS STEM, with hexapolar corrector CEOS).

2.3. Preparation of Plant Extract of Thelypteris glandulosolanosa (Raqui-Raqui), Green Synthesis, and Purification of Silver Nanoparticles with Raqui-Raqui (AgNPs-RR)

Green leaves of *Thelypteris glandulosolanosa* were harvested from the district of Pocsi located in the province and department of Arequipa, Peru, located at 3043 m elevation. Leaves were washed three times using distilled water then washed with Milli-Q water. All the water was removed, and the leaves were sprayed. The leaves sprayed (15 g) were first boiled with 100 mL of Milli-Q water. After cooling to room temperature, the plant extract was filtered through Whatman N$^+$1 filter paper (particle retention: 11 um; filtration speed (Herzberg): 150 s; weight: 87 g/m$^2$) followed by filtration in Millex-GP Syringe Filter Unit, 0.22 μm (33 mm diameter sterile syringe filter with a 0.22 μm pore size hydrophilic
Polyethersulfone membrane). After filtration, the extract was stored at 4 °C for further experiments.

Silver nitrate solutions (0.1 M, AgNO\textsubscript{3}) were also freshly prepared in Milli-Q water under dark conditions as previously described [146]. A range of concentrations of aqueous leaf extracts (5.00, 2.00, 1.00, 0.5, 0.2, 0.1, and 0.05% w/v) were used for the reduction of Ag into Ag\textsuperscript{0} state by mixing it with 0.5 mM AgNO\textsubscript{3}. These mixtures of plant extract and AgNO\textsubscript{3} were temperature controlled under 50 °C with continuous stirring. The reduction of Ag ions in solution was monitored by a visible color change and periodic mixture sampling by measuring in the UV-Visible Gold Spectrum lab 54S (λ 300 to 700 nm). The AgNPs-RR were centrifuged at 12,500 rpm by 15 min, washed three times with Milli-Q water, and finally washed with ethanol. The resulting AgNPs-RR were dried at 40 °C for 48 h.

2.4. Characterization of AgNPs-RR

The AgNPs-RR were characterized to identify their size, shape, surface area, and dispersity. The techniques used in this study to characterize nanoparticles were UV-Visible Spectra, dynamic light scattering (DLS), and scanning transmission electron microscopy (STEM).

2.4.1. UV-Visible Spectra Analysis of AgNPs-RR

The reduction of Ag\textsuperscript{+} ions and formation of AgNPs-RR was monitored by measuring the UV-Visible Spectra of the reaction through a spectrophotometer (Gold Spectrum lab 54S, Rinch Industrial Co., Shanghai, China) at the wavelength range of 300–700 nm (with intervals of 1 nm) using quartz cuvettes. The progress in reducing Ag\textsuperscript{+} ions was monitored by a periodical sampling of the reaction mixture at different reaction times between 0, 15, 30, 45, and 90 min.

2.4.2. DLS and STEM Analysis of AgNPs-RR

The distribution of the size of AgNPs-RR was analyzed by DLS (Zetasizer Nano ZS, Malvern, Worcestershire, UK), and the size of nanoparticle was available in the scanning transmission electron microscopy (JEOL 2200FS STEM, with hexapolar corrector CEOS GmbH, Heidelberg, Germany). The STEM sample was prepared by a drop of reaction sample on the copper-coated grid, and the excess of the solution was removed by drying under a mercury lamp for 5 min as previously described [147].

2.5. Cytotoxicity Assay

MCF-7, A549, and L929 cells were seeded into 96-well plates (1 × 10\textsuperscript{5} cells/well) and incubated with various concentrations of silver nanoparticles (AgNPs) and silver nanoparticles with Raqui-Raqui (AgNPs-RR) (100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 µg/mL) for 48 h at 37 °C in 5% CO\textsubscript{2} humidified incubator. The cytotoxic activity was measured by a methyl thiazolyl diphenyl-tetrazolium bromide (MTT) assay and cell viability percentage was calculated by optical density values subjected in the formula as previously described [148,149].

2.6. Statistical Analysis

All data is represented as mean ± S.E. The statistical analysis was carried out with GraphPad Version 6.01 using one-way ANOVA, statistical significance was examined by Tukey’s post hoc with statistical significance at p-values < 0.05.

3. Results and Discussion

3.1. UV-Visible Spectra Analysis of AgNPs and AgNPs-RR

In this work, the green synthesis of AgNPs-RR was performed using different concentrations (5, 2, 1, 0.5, 0.2, 0.1, and 0.05%) of an aqueous extract of Thelypteris glandulosolanosa (Raqui-Raqui) in a 1:3 stoichiometric relationship as a reduction agent for silver nitrate (0.5 mM). When the colorless solution of AgNO\textsubscript{3} was mixed with Raqui-Raqui,
the bathochromic shift in wavelength maximum and change from colorless to intense yellow indicated the synthesis of AgNPs-RR. UV-Visible further attested to the formation of this nanoparticle, where the broad peak was observed between 420 and 450 nm. In our results, maximum absorption was observed at 450 nm. Although, the spectra were registered at different reaction time intervals, a peak at 420 nm was revealed and reproducible at 0.5% concentration, which suggested that the formed nanoparticles were stable and polydispersed (Figure 1).

![Figure 1. Absorbance of AgNPs-RR.](image)

Kumara Swamy et al. observed the formation of AgNPs at 1 h of incubation with an aqueous extract of *Leptadenia reticulata* [150]. Furthermore, color changes of the reaction mixture have been reported by a reduction of AgNO₃ by the aqueous extract of *Albizia saman* leaf [151]. Additionally, the extract of *Eclipta alba* leaves has been reported to reduce silver ions to silver nanoparticles [152]. An increment of color intensity and surface plasmon resonance (SPR) band sharpness have been reported to indicate the reduction of Ag⁺ into Ag₀ [153]. Additionally, to verify the formation of the AgNPs, the researchers carried out an analysis in a UV-visible spectrophotometer [153]. The analysis showed maximum absorbance close to 420 and 411 nm [153], which is similar to the results in our study. The lack of similarity in observed bioreduction rates is likely a function of leaf extracts from different plant species used as reducing and stabilizing agents. Therefore, the current study contributes to identifying a potential new plant species for the synthesis of silver nanoparticles such as *Thelypteris glandulosolanosa* (Raqui-Raqui).

### 3.2. DLS Analysis of AgNPs-RR

The dynamic light scattering (DLS) analysis was carried out in an aqueous solution to determine the average hydrodynamic size of the AgNPs-RR. Figure 2 shows the size distribution, with a Z-average (d.nm) of 48.11 and polydispersity of 0.472. A characteristic bimodal distribution of nanoparticles is apparent which suggests the possibility of agglomeration in solution (peak 2, 258.1 ± 133.5 nm). A more significant part of the extract was incorporated in the AgNPs (peak 1, 39.16 ± 18.49 nm; peak 3, 7.99 ± 1.06 nm). The area under the curve expresses the proportion of each fraction of AgNPs in the solution, so fraction 1 corresponding to 39.16 ± 18.49 nm presents a more significant proportion of the extract of Raqui-Raqui incorporated in the nanoparticles [154–156]. In contrast, Arya
et al. reported that the average hydrodynamic size of the silver nanoparticles determined by DLS is approximately 54.00 nm [153]. An index polydispersion of 0.2 was reported to the AgNPs biosynthesized using bark extract of Prosopis juliflora indicating that they were homogeneous in size [153]. The polydispersity index (PDI) is the ratio of mass average molecular mass to the number average molecular mass (PDI = Mn/Mw). PDI is used as a measure of broadness of molecular weight distribution. The PDI is a measure of the heterogeneity of a sample based on size. Polydispersity can occur due to size distribution in a sample or agglomeration or aggregation of the sample during isolation or analysis. PDI values < 0.05 are more common to monodisperse samples, while values > 0.7 are common to a broad size (e.g., polydisperse) distribution of particles. The numerical value of PDI ranges from 0.0 (for a perfectly uniform sample with respect to the particle size) to 1.0 (for a highly polydisperse sample with multiple particle size populations) [157]. The PDI was determined to be 0.472. There is no general limit for acceptable polydispersity. In Quality by Design for manufacturing, PDI may or may not be critical for a specification. ISO silver nanoparticles suggest AgNPs with PDI less than 0.5 or 0.1 are considered to be monodisperse and might have less aggregation. AgNPs with PDI > 0.7 or equal to 1 are considered to be polydispersed and might aggregate.

![Size distribution of AgNPs-RR using dynamic light scattering (DLS).](image)

Similarly, Remya et al. reported that the analysis in DLS of the nanoparticles biologically synthesized using the aqueous extract of flower of Cassia fistula showed polydisperse nanoparticles with average size between 21.00 and 30.00 nm [158]. Likewise, Kim et al. reported the particle size distribution analysis by DLS, which comprised a 50–150 nm size range and hydrodynamic diameter of 97 nm with an average size and shape of the nanoparticles confirmed and paralleled the findings obtained from scanning electron microscopy (STEM) analysis [159].

### 3.3. STEM Analysis of AgNPs-RR

Images of the surface size of the purified AgNPs-RR were examined using scanning transmission electron microscopy (STEM). For the analysis, the purified sample was dis-
dispersed by ultrasound in ethanol to form very dilute suspensions and then STEM images of the drops deposited on the coated copper grids carbon were obtained. The AgNPs-RR purified exhibited a quasi-spherical shape and showed aggregation and polydispersity (Figure 3A,B). The size distribution was analyzed using the software ImageJ. The nanoparticles presented a size distribution of 6.64–51.00 nm and an average diameter of 31.45 nm (Figure 3C). This result is similar and is in agreement with the analysis proposed by Jha et al., who reported that the biologically synthesized nanoparticles were spherical and their size ranged between 2 and 50 nm [160]. The average size of the AgNPs-RR analyzed by STEM was smaller than that analyzed by DLS (31.45 nm vs. 48.11 nm). STEM is a direct method of particle size analysis while DLS is an indirect method [154–156]. Differences in methods of analysis from the STEM samples which were evaluated from a dry non-hydrated state that are individually isolated, and the measurement obtained was the surface size of the nanoparticles; on the other hand, DLS evaluates the hydrodynamic size in suspension accounting for an increase in small mean particle size difference between characterization methodology.

Figure 3. Left (A) Image of AgNPs-RR using scanning transmission electron microscopy (STEM). Right (B) Zoomed image of single AgNPs-RR using STEM. (C) Size distribution of AgNPs-RR.
3.4. Cell Toxicity of AgNPs-RR in L929, A549, and MC-F7 Cell Lines

Previous reports suggested that green synthesized AgNPs have greater capacity to suppress cancerous cell growth and have potential for further anti-cancer development as a nanotherapeutic [161–164]. In this work, we examined the cytotoxicity of AgNPs and AgNPs-RR through MTT assay and we observed that the percentage of cell viability decreased dose-dependently with increasing concentration of AgNPs and AgNPs-RR (Figure 4), and the IC\textsubscript{50} value was observed at 12.50 µg/mL for the A549 and MCF7 cell lines.

![Figure 4. Cell viability with AgNPs and AgNPs-RR.](image)

The AgNPs-RR had no apparent cytotoxic to the L929 cell line. Similar dose-dependent responses of AgNPs were reported in a HCT15 cell line with a green synthesis of Vitex negundo [161], in SiHa (human hyper-triploid cervical carcinoma cell line) with green synthesis of Withania coagulans [147] and in human cervical carcinoma cells with green synthesis of Podophyllum hexandrum [165]. Among various species of ferns, Thelypteris torresiana produces protoapigenone that exhibits significant antitumor activity against lung cancer cells (A549) [61], liver cancer cells (Hep G2 and Hep 3B) [58], and breast cancer cells (MCF-7 [62] and MDA-MB-231) [61] with IC\textsubscript{50} values ranging from 0.23 to 3.88 µM [10]. Chang et al. showed that this novel flavone decreased cancer cells viability through the induction of apoptosis [65]. Furthermore, protoapigenone exhibited significant anti-cancer activity in a nude mouse inoculated with human ovarian and prostate cancer cells [65–67].
In our research, we observed the IC\textsubscript{50} at 12.50 \(\mu\)g/mL in the same cellular strains used by Chen et al. [65], Chang et al. [66], and Lin et al. [67]. However, previous studies assessed the activity of protoapigenone extracted from \textit{Thelypteris torresiana}, while we worked with a full aqueous extract of Raqui-Raqui. Ultimately, in vivo detoxification of nanoparticles from a patient’s body is critical for safe and effective nano-based therapy [120]. Filtration and total body clearance of AgNPs from the systemic circulation of cancer patients treated with metallic nanoparticles needs further investigation to minimize cell cytotoxicity as outlined previously [165].

4. Conclusions

A preliminary study of the potential eco-friendly, cost-effective, and convenient green synthesis of novel silver nanoparticles using an aqueous extract of \textit{Thelypteris glandulosolanosa} (Raqui-Raqui) leaves was undertaken. The AgNPs-RR exhibited properties to reduce AgNO\textsubscript{3} solution, an average size of 39.16 nm using DLS analysis and 31.45 nm using STEM analysis. Synthesized AgNPs demonstrated cytotoxicity against cancer cells (A549 and MCF7) and were not cytotoxic in non-cancerous cells. Additional physicochemical characterization studies to further elucidate the particles and follow up biological studies to understand the mechanisms of action of AgNPs-RR and their potential applications and development as delivery systems in vivo are required.

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