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CITRUS PEELS-MEDIATED GREEN FABRICATION OF SILVER NANOPARTICLES: A STUDY ON ANTIBACTERIAL AND CYTOTOXIC EFFICACY

Ayisha Aman Ullah[1]*, Laraib Ilahi[1], Shagufta Noreen[1], Jehan Zaib Arshad[2], Saima Komal[1], Raheela Rahmat Zohra[3]

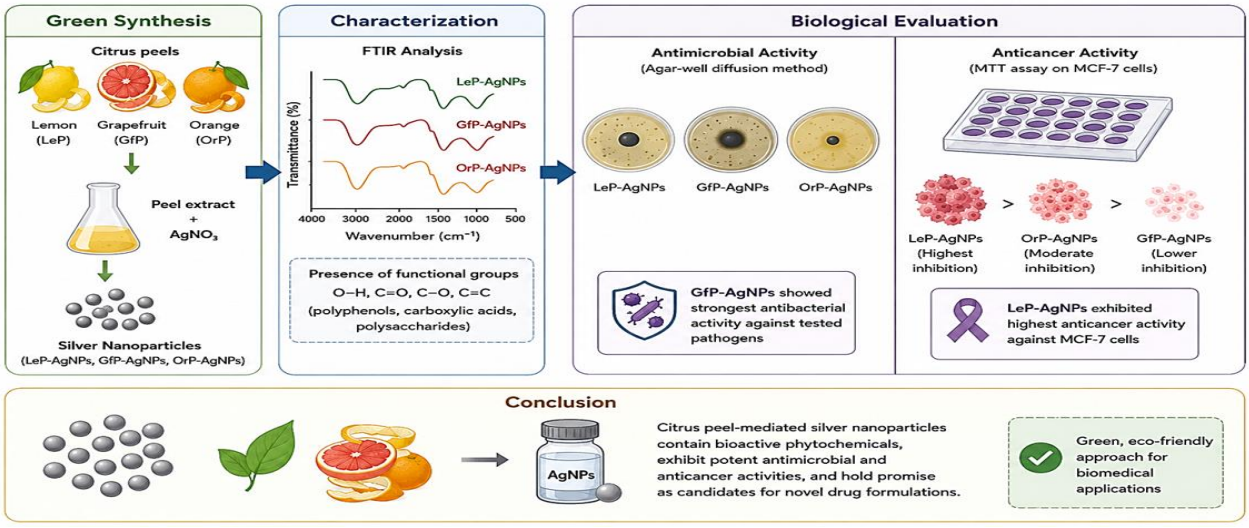
Department of Biotechnology, Jinnah University for Women, Karachi, Pakistan[1]
Department of Physiology, Basic Medical Science Institute, Jinnah Post Graduate Medical Centre, Karachi, Pakistan[2]
Department of Biotechnology, University of Karachi, Karachi, Pakistan[3]

Abstract: Nanotechnology has emerged as a versatile approach for the synthesis of nanomaterials, with green synthesis gaining considerable attention as an eco-friendly and sustainable method. Plant-based synthesis utilizes readily available, low-cost, and less hazardous plant extracts rich in bioactive compounds for the efficient production of nanoparticles. The objectives of current research were to fabricate silver nanoparticles using peels of various citrus fruits including lemon, grape fruit and orange and to exploit their biotherapeutic effects specifically antimicrobial and anticancer efficacy. Synthesized-nanoparticles were screened for antimicrobial activity using agar-well diffusion method. For cytotoxicity evaluation of silver nanoparticles, MTT assay was used on Human Breast Cancer Cell Lines (MCF-7). FTIR was done to assess the functional groups in fabricated nanoparticles. According to antimicrobial profiling of citrus fruit peel extracts, it was noticed that GfP-AgNPs (grape fruit) exhibited strong antibacterial activity against *Escherichia coli*, (30.33 ± 0.44 mm), *Klebsiella pneumoniae* (29.8 ± 0.85 mm) and *Enterococcus faecalis* (30.7 ± 0.86 mm) as compared to LeP-AgNPs (lemon) and OrP-AgNPs (orange). Cytotoxicity analysis revealed that LeP-AgNPs (100 µg/mL) displayed highest inhibition (84.24 %) with declined malignant cell viability of 15.76 ± 0.10 %, > OrP-AgNPs with inhibition rate of 75.35% and 24.65 ± 0.26 % cell viability> GfP-AgNPs with 73.16% inhibition and 26.84 ±0.13% cell viability. FTIR spectra of all synthesized silver nanoparticles from citrus fruit peel extracts showed the presence of polyphenols, alkaloids, and polysaccharides. The study demonstrated that silver nanoparticles synthesized from citrus fruit peels possess significant potential as promising candidates for novel drug formulations. However, it is extremely important to carry out a full range of *in vivo* studies to validate the results and ensure that the synthesized silver nanoparticles are safe, bio-compatible, and have no toxicological effects on animals.

Key words: Antibacterial, citrus fruit peels, silver, nanotechnology, nanoparticles cytotoxicity

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Graphical Abstract



INTRODUCTION

Nanotechnology has advanced significantly, with the development and utilization of nanomaterials becoming a major focus across various scientific and industrial fields. One of these materials is silver nanoparticles (AgNPs), which have attracted widespread interest for their antimicrobial and cytotoxic properties, as well as their compatibility with medicine, environmental clean-up, and industrial applications. (Eker *et al.*, 2025). Much work has been done on the use of AgNPs in medical technology, including wound dressings, coating of medical instruments, and drug delivery (Sharma *et al.*, 2020).

However, the conventional techniques of AgNPs synthesis, despite having many benefits, often employ the use of toxic reducing agents like sodium borohydride, hydrazine, and other toxic substances, which are harmful to the environment and human health (Mittal *et al.*, 2013). The conventional techniques also result in the production of toxic by-products hence making it necessary to develop alternative approaches for AgNPs synthesis that are eco-friendly. The green synthesis method is one of the most promising and sustainable approach for AgNPs synthesis. This technique utilizes biological components such as plant extracts and microorganisms to reduce and stabilize silver nanoparticles (Iravani *et al*., 2014).

Several biological materials have been reported as promising candidates for green synthesis. Plant extracts are rich in bioactive compounds such as flavonoids, polyphenols, alkaloids, tannins, terpenoids and organic acids, which can act as natural reducing and capping agents. Phytochemicals present in plant extracts have the ability to reduce silver ions (Ag^+) to metallic silver (Ag^0) nanoparticles . Phytochemicals can also serve as natural capping agents to enhance the stability and functionality of nanoparticles (Ahmed *et al*., 2016). Among other green methods, the plant-mediated synthesis is especially valued for its simplicity, low cost, and possibility to produce stable nanoparticles with enhanced biocompatibility (Iravani *et al*., 2014). For example, peels of *Citrus tangerina* (tangerine), *Citrus sinensis* (sweet orange) and *Citrus limon* (lemon) have been found as one of the best sources for the green synthesis of AgNPs. The peels of citrus fruits contain a high amount of bioactive substances which may improve the synthesis process and bioactivity of nanoparticles (Keskin *et al*., 2023).

The emergence of antimicrobial-resistant pathogens has become a crucial global problem, which poses a serious threat to human health and necessitates the development of alternatives to conventional antibiotics. According to World Health Organization, antimicrobial resistance (AMR) causes approximately 1.27 million deaths every year and according to its projections, by 2050, AMR may cause 10 million deaths annually. Traditional antibiotics, which once have been highly efficient for treating bacterial diseases, now became less effective due to fast adaptation and evolution in bacteria (Ventola, 2015). AgNPs synthesized from plants demonstrate broad spectrum antimicrobial activity as they affect both Gram-positive and Gram-negative bacteria. Another significant medical application of nanotechnology is the assessment of the cytotoxicity of green-synthesized nanoparticles.The GLOBOCAN (report on global burden of cancer) 2018 estimates that in 2018, there were 18.1 million new cancer cases and 9.6 million cancer deaths worldwide. This high incidence and mortality rate underscore the urgent need for the development of novel and effective therapeutic agents for cancer treatment (Bray *et al.*, 2018). Citrus fruit peels, specifically their flavonoid content, have been characterized as a rich and valuable source of bioactive compounds with potential applications in cancer treatment. Previous studies have shown that flavonoids obtained from citrus peels can influence several important cellular processes, including cell proliferation, cell cycle regulation, apoptosis, metastasis, and angiogenesis. Recent molecular studies have further provided insights into the cell signaling pathways involved in the anticancer effects of these compounds. Together, these findings highlight the potential of citrus peel extracts as chemopreventive agents and support further investigation of their therapeutic properties, particularly those of isolated and purified flavonoids (Koolaji et al., 2020). Therefore, this research focuses on the green synthesis of AgNPs by using peel extracts of *Citrus paradisi* (grapefruit), *Citrus sinensis* (sweet orange), and *Citrus limon* (lemon) peels, followed by screening their antibacterial properties and cytotoxicity against cancer cells.

MATERIALS AND METHODS

Collection and Pretreatment of Citrus Fruit Peel

In the present study, citrus fruit peels such as lemon (*Citrus limon*), orange (*Citrus sinensis*), and grapefruit (*Citrus paradisi*) peel were collected from juice stores. These peels were brought to the laboratory and washed using distilled water to eliminate dust particles. The peels were further chopped into small pieces (1–2 cm) to fasten their drying process and make the extraction process easy (Iravani *et al*., 2014). The peels were evenly spread out and sun-dried for 2-3 hours.

Preparation of extract from citrus peels

Aqueous extraction method was adopted in order to extract bioactive ingredients that aid in reducing and stabilizing the silver nanoparticles. Eight grams of dehydrated citrus peels were placed in 80 ml of distilled water in a 250 ml glass beaker. The mixture was heated to 100 degrees Celsius for ten minutes in order to extract the bioactive components (Durán *et al.*, 2016). The mixture was later cooled down and passed through a filter paper (Whatman no. 1) with a diameter of 11.00 µm. This enabled separation of the solid ingredients while the filtrate containing polyphenols and flavonoids was collected.

Synthesis of silver nanoparticles using extracts of citrus fruit peels

1 mM solution of $AgNO_3$ was prepared in 50 mL of distilled water. The solution was continuously stirred for 15 minutes using a magnetic stirrer to ensure complete dissolution of silver ions (Iravani *et al.*, 2014). The prepared $AgNO_3$ solution was stored in an amber-coloured bottle to prevent photodegradation, as silver ions are highly sensitive to light exposure (Sharma *et al*., 2020). For the synthesis of silver nanoparticles, 3 ml of

citrus peel extract was added dropwise into 50 mL of 1 mM $AgNO_3$ solution while continuously stirring the mixture. The reaction mixture was covered with aluminum foil and stored at room temperature in the dark for 24 hours to prevent unwanted photochemical reactions. The conversion of silver ions (Ag^+) to silver nanoparticles (Ag^0) was evidenced by color change from pale yellow to dark brown, which is a typical sign of AgNPs synthesis (Kumar *et al.*, 2020).

Fourier Transform Infrared Spectroscopy

The functional groups involved in the capping and stabilization of the agents used in the production of AgNPs were studied through FTIR spectroscopy from 400 cm^{-1} to 4000 cm^{-1}.

Antibacterial potential of synthesized silver nanoparticles

The antibacterial activity of AgNPs was tested against five common bacterial pathogens: *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* (Gram-negative) and *Staphylococcus aureus*, *Enterococcus faecalis* (Gram-positive). These bacterial strains were selected due to their clinical significance and resistance to conventional antibiotics. Initially, the pathogenic cultures were grown on nutrient agar plates. Then isolated colony was inoculated in tryptic soy broth, followed by incubation at 37 °C with shaking at 180 rpm for 18 hours. An analysis of bacterial growth was done spectrophotometrically at 600 nm using a UV-Vis spectrometer. McFarland standard (0.5) was used to adjust the concentration of cell suspension to 1.0×10^6 CFU/ ml.

The study employed the agar well diffusion technique to test the ability of synthesized AgNPs to inhibit bacterial growth. A sterile Nutrient Agar plate was prepared and allowed to solidify under sterile conditions. Four holes of 6 mm diameter were made on the nutrient agar surface using a sterile cork borer. The wells were loaded with 50 µl citrus peels mediated AgNPs (10 µg/mL), $AgNO_3$, citrus peel extracts, and Distilled Water (Negative Control); the plates were incubated at 37° C for 24 hours; and subsequent to incubation, the diameter of the inhibition zone was measured to determine AgNPs bactericidal activity (Durán *et al*., 2016).

Cytotoxicity screening of Synthesized Silver Nanoparticles

To assess the cytotoxicity of materials, standard colorimetric assay (MTT assay) is used to determine the viability of cells. In the cytotoxicity assay, breast cancer cell lines (MCF-7) were used to assess the effectiveness of AgNPs on cancer cells (Raj *et al.* 2020). Cell lines were obtained from a cell culture repository and maintained according to protocol (Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% Penicillin/Streptomycin at 5% CO_2 incubator at 37°C). A total number of 5 x 10^4 cells of each cell line were plated into 96-well culture plates and allowed to adhere for 24 hours prior to treatment. Following the 24-hour time period, a fabricated solution (100 µg/mL) of AgNPs was added to each of the plates and incubated for 24 to 48 hours. Non-treated cells served as the negative control and doxorubicin (an established cytotoxic drug) was used as positive control (Mahmoudi *et al*. 2011). After incubation, 10 µL of MTT reagent (5 mg/mL) was added to each well and incubated for an additional 4 hours. The formazan crystals created were solubilized using DMSO and the absorbance was measured at 570nm using a microplate reader. The percentage of cell viability was calculated using equation 1; a decrease in the cell percentage denotes cytotoxicity.

$$\textbf{\% Viability} = \frac{AT}{AC} \times 100 \qquad \textbf{(eq 1)}$$

Where AT represents optical density of treated samples and AC highlights absorbance of control sample.

Statistical Analysis

All the experiments have been performed in three replicates. Data has been presented in terms of mean of duplicates ± standard error. Standard deviation and standard error were calculated using Microsoft Excel 2017 version.

RESULTS AND DISCUSSION

FTIR Analysis of synthesized nanoparticles

FTIR spectroscopy of GfP-AgNPs, LeP-AgNPs, and OrP-AgNPs (400–4000 cm^{-1}) revealed characteristic absorption bands at ~3200–3400 cm^{-1} (O–H/N–H stretch), ~2850–2950 cm^{-1} (C–H stretch), ~1600–1650 cm^{-1} (C=O/C=C, carboxylate stretch), ~1350–1450 cm^{-1} (COO^- symmetric stretch/O–H bend), and ~1000–1150 cm^{-1} (C–O–C stretch), confirming the presence of bioactive compounds such as proteins, polyphenols, alkaloids, and polysaccharides involved in AgNP synthesis (Mafhala et al., 2024). The hydroxyl and carbonyl groups act as electron donors, reducing Ag^+ to Ag^0 through redox reactions to form the nanoparticles (Abuzeid et al., 2023). Peak shifts from 3292 cm^{-1} to 3489 cm^{-1} and 1263 cm^{-1} to 1395 cm^{-1} following bioreduction indicate direct interaction between Ag ions and phytochemical functional groups, confirming their role in capping and stabilizing the nanoparticles (Mafhala *et al*., 2024; Dipankar & Murugan, 2012). Among the three, OrP-AgNPs showed the strongest absorption bands, indicating higher phytochemical content and greater antioxidant activity from polyphenols. GfP-AgNPs displayed intermediate peak intensities, reflecting a balanced phytochemical profile enriched in citric acid. LeP-AgNPs showed the weakest bands but the highest transmittance (>97%), suggesting a purer nanoparticle product with less residual organic capping material. This pattern aligns with earlier findings that adsorbed biomolecules form a stabilizing layer preventing agglomeration through steric and electrostatic interactions, conferring colloidal stability (De Barros et al., 2018). The FTIR results confirm the efficiency of citrus-peel-mediated green synthesis and highlight the extract-specific role of phytochemicals in nanoparticle formation and stabilization.

Table 1: Antibacterial activity of synthesized GfP-AgNPs (Grape fruit peels)

Pathogenic Microb	Zone of Inhibition (mm)		
	$AgNO_3$	GfP-AgNPs	Extract
Escherichia coli	0.7 ± 0.15	30.33 ± 0.44	20.25 ± 0.12
Klebsiella pneumoniae	14.1 ± 0.69	29. 8 ± 0.85	7.10 ± 0.56
Enterococcus faecalis	26.7 ± 0.14	30.7 ± 0.86	14.70 ± 0.34
Proteus mirabilis	30.3 ± 0.24	22.8 ± 0.60	13.23 ± 0.16
Staphylococcus aureus	20.4 ± 0.12	12.6 ± 0.08	NA

Table 2: Antibacterial activity of synthesized LeP-AgNPs (Lemon peels)

Pathogenic Microbe	Zone of Inhibition (mm)		
	$AgNO_3$	LeP-AgNPs	Extract
Escherichia coli	10.3 ± 0.63	10.9 ± 0.15	NA
Klebsiella pneumoniae	18.7 ± 0.05	22.6 ± 0.44	11.5 ± 0.28
Enterococcus faecalis	11.2 ± 0.37	20.2 ± 0.14	NA
Proteus mirabilis	22.2 ± 0.14	30.3 ± 0.44	10.6 ± 0.12
Staphylococcus aureus	10.4 ± 0.08	20.8 ± 0.64	2.2 ± 0.24

Table 3: Antibacterial activity of synthesized OrP-AgNPs (Orange peels)

Pathogenic Microb	Zone of Inhibition (mm)		
	$AgNO_3$	OrP-AgNPs	Extract
Escherichia coli	10.5 ± 0.02	10.5 ± 0.05	NA
Klebsiella pneumoniae	19.8 ± 0.30	10.5 ± 0.05	NA
Enterococcus faecalis	20.5 ± 0.28	18.9 ± 0.73	10.78 ± 0.26
Proteus mirabilis	10.5 ± 0.03	20.4 ± 0.23	10.8 ± 0.28
Staphylococcus aureus	14.5 ± 0.23	21.2 ± 0.66	11.2 ± 0.11

Antibacterial Effectiveness of Silver Nanoparticles

The synthesized silver nanoparticles of citrus fruits peels provoked significant antibacterial activity against both gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis*) and gram-positive bacteria (*Staphylococcus aureus and Enterococcus faecalis*). The Table 1-3 summarizes the antibacterial activity**.** AgNPs synthesized from grapefruit peels (GfP-AgNPs) demonstrated high antibacterial activity against *Escherichia coli, Klebsiella pneumoniae* and *Enterococcus faecalis.* Extract of grape fruit peels also solely exhibited inhibition activity against all pathogens except *Staphylococcus aureus.* On the other hand, AgNPs synthesized from lemon peels (LeP-AgNPs) showed strong antibacterial activity against all indicator pathogens except *Escherichia coli.* While lemon peels extract was unable to display antibacterial activity. Conjugation of lemon peels extract with silver nitrate improved its bioactivity.

AgNPs synthesized from orange peels (OrP-AgNPs) exhibited the highest antibacterial activity against *Proteus mirabilis* and *Staphylococcus aureus* (Figure 2). Among all AgNPs of citrus fruit peels, GfP-AgNPs possessed greater antimicrobial potential as compared to others. Several previous studies validate and favor the consequences of current research. For instance, Arsène, *et al*. (2021) also showed significant antibacterial activity of grape fruit peels-based nanoparticles against both Gram-positive and Gram-negative bacteria. Nanoparticles synthesized from orange, grapefruit and lemon peels exhibited effective antimicrobial activity against multi drug resistant clinical pathogen *Staphylococcus aureus* (Castañeda-Aude *et al*., 2023). Gupta *et al* (2025) demonstrated that orange peel nano-particles displayed maximum inhibitory effects against *Bacillus subtilis* and *Staphylococcus aureus*. Nanoparticles of citrus peel extracts such as Key lime, Cleopatra mandarin, Persian lime and grape fruit were proved to be promising candidates for phytosynthesis of nanoparticles for antimicrobial properties as they possessed considerable inhibition against *Staphylococcus aureus, Listeria monocytogenes, Bacillus cereus and Escherichia coli* O157:H7 (Alsakhawy *et al*., 2022; Mickky *et al* 2024; Nahar *et al* 2021; Alkhulaifi *et al* 2020).

Cytotoxic effects of the fabricated AgNPs

The cytotoxic effects of the green-synthesized AgNPs was evaluated on Human Breast Cancer Cell Lines (MCF-7). All AgNPs synthesized from Citrus fruit peels have shown considerable cytotoxic effects on breast cancer cell lines. The LeP-AgNPs (100 µg/mL) demonstrated highest percent inhibition (84.24 %) with reduced malignant cell viability of 15.76 ± 0.10 %, followed by OrP-AgNPs with percent inhibition 75.35% and 24.65 ± 0.26 % cell viability. GfP-AgNPs showed comparatively lower effects with 73.16% inhibition and 26.84 ±0.13% cell viability (Table 4). Alkhulaifi *et al.* (2020) also reported that AgNPs synthesized from the Citrus limon peel had cytotoxic properties against MCF-7 and HCT-116 cells. Furthermore, AgNPs produced from orange peels inhibited the proliferation of both HCT-116 (IC50 of 16 ppm) and HepG2 (IC50 of 1.6 ppm) cells. Similar effects were noted in other experimental studies (George *et al.* 2024; Mafhala *et al.* 2024; Park *et al*. 2010; Palaniappan *et al*. 2015; Dhand *et al*. ;2016). At 100 µg/mL, the synthesized AgNPs exhibited marked cytotoxic activity against the tested malignant cell line, indicating promising preliminary anticancer potential.

Table 4: Cytotoxic effects of synthesized AgNPs on MCF-7 cell lines

Samples	Conc. (µg/mL	% Inhibition	% Viability (Mean ± SD)
GfP-AgNPs	100	73.16	26.84 ±0.13
LeP-AgNPs	100	84.24	15.76 ± 0.10
OrP-AgNPs	100	75.35	24.65 ± 0.26
Doxorubicin (positive control)	100	90.46	9.54 ± 0.02

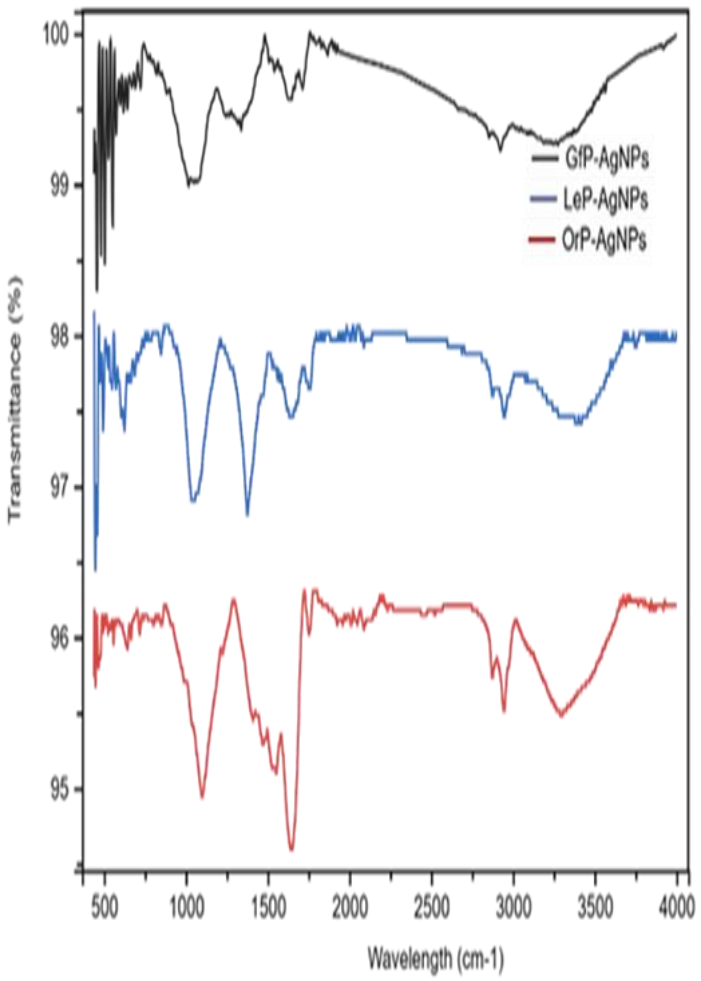


Figure 1: Comparative FTIR transmittance spectra of nanoparticles synthesized using citrus fruit peel extracts

The cytotoxicity of silver nanoparticles (AgNPs) is most likely due their ability to induce reactive oxygen species (ROS) generation in cells thereby causing cell death (Venugopal *et al*. 2017). Multiple studies have suggested that AgNPs may affect the mitochondria and disrupt electron transport chain thereby increasing levels of intracellular ROS (Park *et al*. 2010; Singh & Ramarao, 2012). The oxidative stress induced by excessive levels of ROS is crucial to play a key role in AgNPs-induced cellular toxicity.

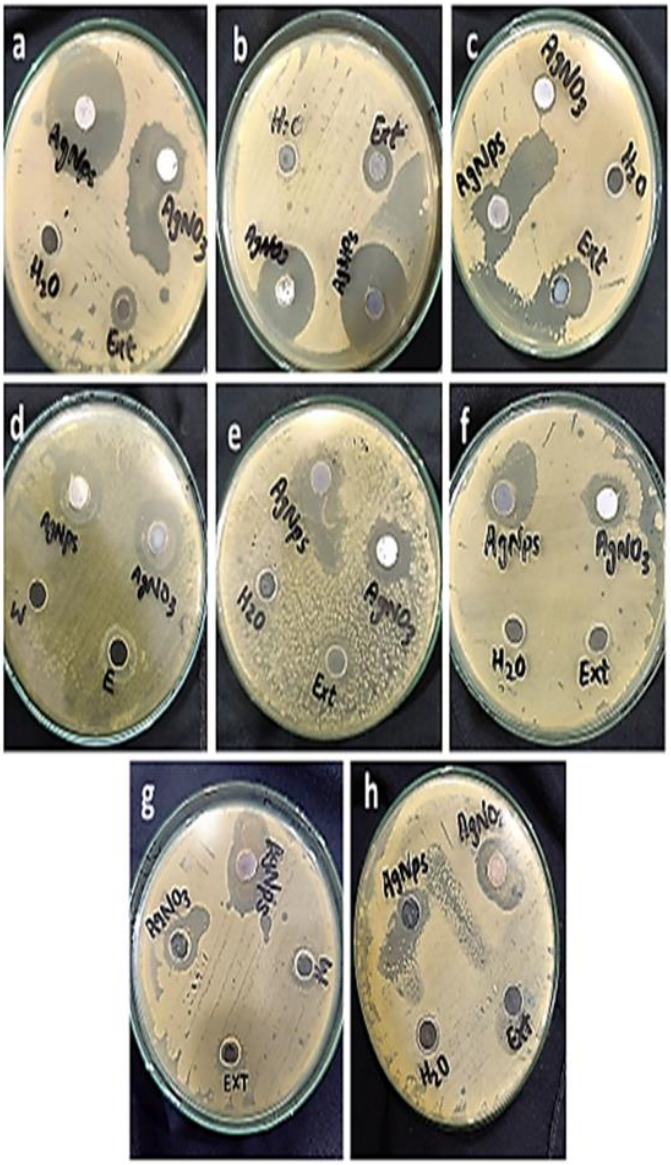


Figure 2: Antimicrobial activity of AgNPs: Grape fruit peels (a) *Klebsiella pneumoniae*, (b) *Enterococcus faecalis*, (c) *E.coli*; Lemon peels (d) *Klebsiella pneumoniae* (e) *Proteus mirabilis* (f) *Staphylococcus aureus*; Orange peels (g) *Proteus mirabilis* (h) *Staphylococcus aureus*

Furthermore, the enhanced anticancer activity of AgNPs may be due to a synergistic interaction between the nanoparticles and surface-associated polyphenols. Cancer cells are susceptible to nanoparticle uptake when compared to normal cells because of the difference in metabolic activities and fast proliferation rates making them more vulnerable (Cairns *et al*., 2011). Moreover, the combination of AgNPs and polyphenols does not only result in ROS production but could also inhibit transcriptional pathways within the cell (Figure 3).
Importantly, polyphenols are selectively toxic, mainly targeting diseased cells and leaving healthy cells intact (Li *et al*., 2006).

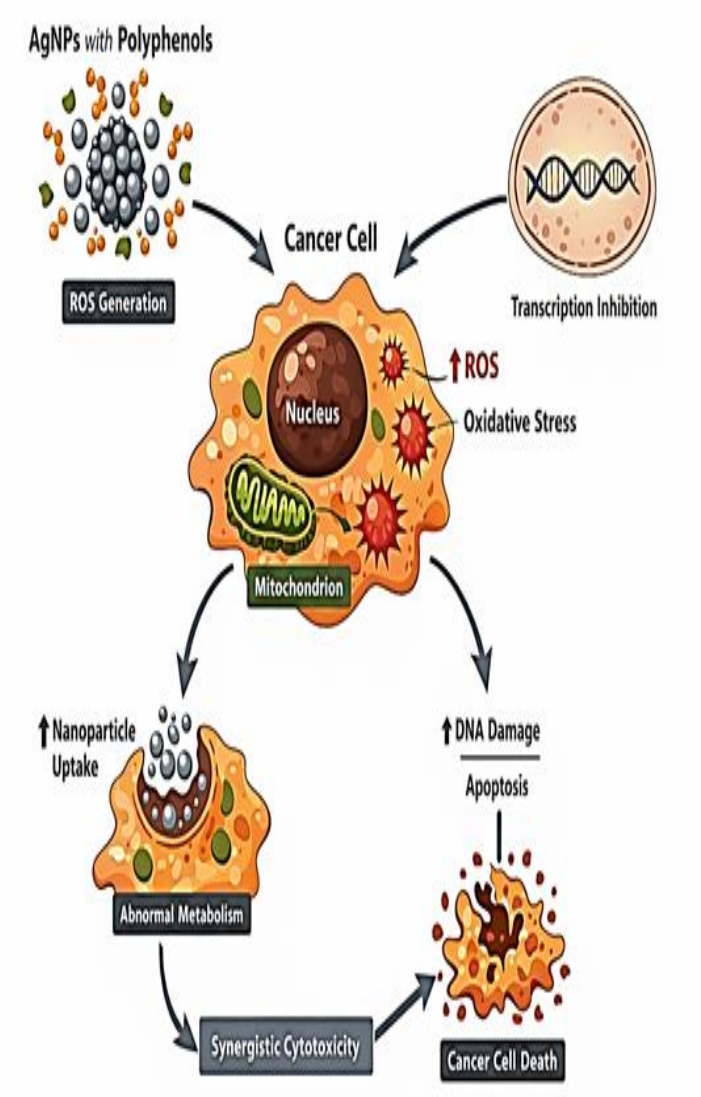


Figure 3: Role of AgNPs in cancer therapy

Doxorubicin, a commonly used anticancer agent, was used as a positive control in this study with maximal inhibition of 90.46%. Even though the doxorubicin had better cytotoxic effects, the small difference between both drugs makes it clear how the potential of green synthesized nanoparticles can be utilized in the fight against cancer. It is worth noting that in spite of the fact that there is toxicity and side effects of doxorubicin, the high efficacy of the green synthesized nanoparticles shows its great potential in comparison to conventional chemotherapeutic agents. It should be stated that silver nanoparticles have the unique ability to induce cell death through apoptosis making it possible to use them as chemotherapeutic agents. Thus, it can be concluded that AgNPs created via plants have good potential in creating new anticancer drugs. However, comprehensive investigations are still required to thoroughly evaluate the efficacy and safety of these nanoparticles prior to their clinical translation. Overall, this study provides valuable insights into the therapeutic potential of plant-derived AgNPs against cancer cells and paves the way for further exploration in this field.

CONCLUSION

This study reveals that biosynthesis of silver nanoparticles utilizing extracts from peels of different citrus fruits can be considered as an effective, environmentally friendly and cost-effective way of nanoparticle preparation. The use of agricultural waste can be viewed as a sustainable practice that follows the principles of green nanotechnology. The biosynthesized nanoparticles showed pronounced antibacterial effect against various pathogens and, thus, can be regarded as promising agents that might serve as alternatives to the antimicrobials to overcome global AMR issue. Moreover, increased cytotoxic effect against cancer cells was observed and confirmed by MTT assay which proves their potential for use in anticancer therapy. However, these findings are based on *in-vitro* experiments at a limited concentration and should not be interpreted as evidence of therapeutic efficacy. The synthesis approach may have potential for further development, although its scalability and commercial feasibility require additional investigation. Similarly, the observed antimicrobial activity suggests possible applications in environmental and water-treatment technologies, which require further validation. These findings support the potential of citrus peel-mediated AgNPs as multifunctional nanomaterials, while further dose-dependent, mechanistic, toxicity, selectivity, and *in-vivo* studies are required to establish their safety, efficacy, and practical applications.

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Corresponding author
Dr. Ayisha Aman Ullah
Department of Biotechnology,
Jinnah University for Women, Karachi, Pakistan
E.mail: ayisha.aman@juw.edu.pk