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Effect of biosynthesized silver nanoparticles by *Garcinia mangostana* extract against human breast cancer cell line MCF-7

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Abstract

Breast cancer is the greatest common malignancy in females. This syndrome represents a serious public health problem that needs additional study to define its prediction and specific treatment. MCF-7 is a usually used breast cancer cell line that has been spread for many years by multiple groups. It shows to be a suitable model cell line for breast cancer studies worldwide, including those concerning anticancer. Anticancer and anti-inflammatory influences are important to treat the threats of chronic inflammation related with chronic diseases. Natural products have made and are remaining to make vital influences to the search for new anticancer agents. The use of natural foodstuffs in relationship with green nanoparticles has drawn attention because of its easy and eco-friendly protocol. Therefore, we aimed to investigate the antiproliferative activity of silver nanoparticles biosynthesized by mangosteen peel extract (MPE) on human breast cancer cell line (MCF-7) using [3-(4, 5-dimethylthiazolyl)-2, 5-diphenyl-tetrazolium bromide (MTT) method. In the present study serial concentrations (5, 10, 15, 50, 70, µg/mL) of cells biosynthesized silver nanoparticles by (MPE) was tested against MCF-7 cell lines showed a cytotoxic effects, morphological degeneration, damaging and has more effectiveness against breast cancer cells. The results showed a substantial a high reducing power, a sensible antiproliferative role and antioxidant activity. The results showed that silver nanoparticles biosynthesized by mangosteen peel extract (MPE) can be regarded as a suitable candidate for designing anticancer pharmaceutical preparations.

Keywords: MCF-7 cell line; *Garcinia mangostana*; nanoparticles; antioxidant.

Practical Application: Silver nanoparticles biosynthesized by mangosteen peel extract (MPE) can be used as anticancer.

1 Introduction

Breast cancer is a long-lasting disease and may be a heterogeneous group of neoplasms originating from the epithelial cells lining the milk ducts or in milk lobules. That increase in the prevalence of cancer cases globally has attributed many factors such as exposure to, pollution, ultraviolet light obesity and smoking habits. Cancer is considered a group of distinct diseases are the most important causes genetic mutations in a single cell. and can Ngswalkhalaaa tumor surrounding tissue (Elenbaas et al., 2001; Moattar et al., 2015).

MCF-7 cells are useful for in vitro breast cancer studies because the cell line has retained several ideal characteristics particular to the mammary epithelium. These include the ability for MCF-7 cells to process estrogen, in the form of estradiol, via estrogen receptors in the cell cytoplasm. This makes the MCF-7 cell line an estrogen receptor (ER) positive control cell line (Portokalakis et al., 2016; Santos et al., 2022; Tang et al., 2022).

Garcinia mangostana is a tropical fruit, originally grows in Southeastern Asian countries mostly Malaysia, Indonesia, and Thailand. It is very rich of some bioactive compounds such as chemical, physical, and medical properties, α-Mangostin (AMG) is a strong anticancer xanthone that was discovered in mangosteen, were found in very high amount of biological functions mostly being antioxidant. AMG possesses the highest occasion for chemotherapeutic and inhibits every step in the process of carcinogenesis (Wahab et al., 2012; Rajakannu et al., 2015; Buttacavoli et al., 2018).

Advances in nanotechnology have provided a new way of improving drug delivery systems (DDS) for hydrophobic drugs. At the identical time, there are only limited studies within the cytotoxic effects of biologically synthesized AgNPs, against neoplastic cell lines. MTT assay was accustomed assess the effect of AgNPs on proliferation of MCF-7 cells and HBL-100 cells. This is often the primary study to report the cytotoxicity of AgNPs

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synthesized employing a. squamosa against cancer cell lines (MCF- 7) (Zulkifli et al., 2020; Al-Khedhairy & Wahab, 2022).

Nanoparticle drug delivery system is used to reduce the lack of selectivity of anticancer drugs. Most cancer chemotherapeutics are administered either orally or intravenously to realize systemic distribution for effective treatment. Though, as a reason of the lack of selectivity, these drugs cause significant damage to rapidly proliferating normal cells. The key goal of targeted therapies is to effort on the chemotherapeutics to cancer cell which ultimately reduce the side effects (Venugopal et al., 2017; Khan et al., 2019; Priya et al., 2020). Most of the studies reported that silver nanoparticles (AgNPs) with much plant extraction showed significant toxic effects with inhibitory concentration of 50% in breast cancer cell lines, while less toxicity were reported in normal cell lines (Al-Radadi, 2021; Madakka et al., 2021; Huq et al., 2022). Therefore, in the present study, we investigated the Investigate the effectiveness and determination of morphological changes of *G. mangostana* extracts in association with nanotechnology against MCF-7 breast cancer cell line through cytotoxicity (MTT assay).

2 Materials and methods

2.1 Plant material

Fresh *G. mangostana* fruit was collected from the a hypermarket at Riyadh City, Saudi Arabia, and carefully washed with deionized water several times to remove dust particles.

2.2 Extract preparation and isolation

The rind of fruit was separated to two parts: the first part was air-dried to remove the residual moisture, cut into small pieces, and stored in air-tight container. The second part was cut into small pieces, loaded onto a tray, and freeze- dried the a shelf in a freeze dryer (Labconco 8811 Prospect Ave, Kansas City, MO 64132, USA). Both parts were ground to a powder for further extractions.

2.3 Synthesis of nanoparticles using the peel of G. mangostana

Green silver nanoparticles were synthesized by bio reduction of Ag+ by using fresh suspension of *G. mangostana* fruit. 5 mL of the extract was added drop by drop to an aqueous solution of AgNO3 (50 mL, 0.1 mM/mL) and was stirred at 45-50 °C for 30 min. The ultrasonication was applied to the mixed solution for 3 h. Silver nitrate solution color was changed from colorless solution to deep brown, indicating the formation of Ag-NPs. The residual AgNO3 was removed by dialysis against deionized water at 4 °C. The formed Ag-NPs have been analyzed by Zeta sizer (ZEN 3600, Malvern, UK) and characterized using transmission electron microscopy (TEM) (JEM-1011, JEOL, Akishima, Japan). Furthermore, the green silver nanoparticles synthesis was confirmed by UV-Vis spectrophotometer in the range of 200-1000 nm wavelength. The absorption spectra were recorded with Perkin-Elemer Lambda 40 B double beam spectrophotometer using 1 cm matched quartz cells.

2.4 MCF-7 culture and maintenance

MCF-7 cells were cultured in Dulbecco's Modified Eagle's medium DMEM supplemented with 10% FBS, 1% Penicillin/ Streptomycin and 1% L-glutamine in 75ml flasks under aseptic technique, at 37° C in 5% CO_2 incubator. Culturing took place in 2 weeks, sub-culturing was done by removing old media, washing with 5 mL of PBS, cells were detached from surface using 4 mL trypsin replacement enzyme (Gibco TrypLE™ Express), incubated for 5 min, after cells are detached and checked under the inverted microscope, 6 mL of complete culture media was added in the 75 mL-flask, 3 mL of the cell suspension in was divided as 1 mL each in 3 flasks filled with 11 mL of complete culture media, leaves 7 mL of cell suspension cryopreserved.

2.5 Automated cell counting

Cell were counted using BIO-RAD automated cell counter which accurately counts cells in one simple step using innovative auto-focus technology and a sophisticated cell-counting algorithm to produce accurate cell counts in less than 30 seconds using special 2-chamber glass slides and trypan blue dye.

2.6 Cell plating in 96-well plates

Cells were seeded in 96-well plates at a density of 1×10^4 cells/ well and incubated at 37° C in 5% CO2 incubator. Cells in each well reached 80% confluency after 24 h of incubation.

2.7 Experimental design

Cells were seeded in 96-well plates at a density of 1×10^4 cells/ well with complete media, labeled as 2 plates for 24 h dose and another 2 plates for 48 h dose and incubated at 37 °C in 5% CO2 incubator. After 24 h of incubation, cells were checked under an inverted microscope, complete media was discarded from each well, cells were washed with 200 µL/well PBS solution then discarded, 200 µL of serum-free DMEM media was added with Serial dilutions of (2, 5, 10, 15, 20, 50, 70, 100 µg/mL) which was made from 5 mg/mL stock concentration of biosynthesized silver nanoparticles by *G. mangostana* extract.

96-well plate layout as follows:

Plate 1 (24 h dose):

Group 1-First raw seeded with MCF-7 cells without treatment dose (control).

Group 2-Second raw (5 µg/mL conc.)

Group 3-Third raw (10 µg/mL conc.)

Group 4-Fourth raw (15 µg/mL conc.)

Group 5-Fifth raw (50 µg/mL conc.)

Group 6-Fourth raw (70 µg/mL conc.)

Seventh raw (blank) [serum-free DMEM media with no cells]

Plate 2 (48 h dose):

Group 1-First raw seeded with MCF-7 cells without treatment dose (control).

Group 2-Second raw (5 µg/mL conc.)

Group 3-Third raw (10 µg/mL conc.)

Group 4-Fourth raw (15 µg/mL conc.)

Group 5-Fifth raw (50 µg/mL conc.)

Group 6-Fourth raw (70 µg/mL conc.)

Seventh raw (blank) [serum-free DMEM media with no cells]

2.8 MTT assay (cell viability)

This test is used to measure the metabolic activity of cells and as an indicator of cell viability, proliferation and cytotoxicity. This colorimetric assay is based on the reduction of a yellow tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide or MTT) to purple formazan crystals by metabolically active cells.

2.9 MTT assay procedure

MTT assay was carried out according to the method by (Mosmann, 1983) . Target cells were prepared with treatment and cultured in 96-well plate with final volume of 200 µL/well, then incubated for 24 h in 37 ˚C, 5% Co_2 incubator. After the incubation period old media and treatment doses were discarded from each well, then washed each well with 100 µL PBS solution and discard, 100 µL of serum-free medium was added with 10 µL of MTT solution in each well, to achieve a final concentration of 0.45 mg/mL. After that plates were incubated in 37 ˚C, 5% Co_2 incubator for 4 h, media and MTT solution was removed from each well and 100 µL of Dimethyl sulfoxide (DMSO) was added in each well, and placed inside the shaker for 15 min, the absorbance was measured at 570 nm by using a microplate reader (Biotek, ELX 800, USA). This procedure was performed in the dark.

2.10 Statistical analysis

Results represent means ± standard errors of the means (SEM). Data were analyzed using the one-way analysis of variance (ANOVA). For comparison of significance between groups, Duncan's test was used as post hoc test according to the Statistical Package for the Social Sciences (SPSS version 20.0 IBM, Armonk, NY, USA).

3 Results

3.1 Characterization of silver nanoparticles with G. mangostana

The biosynthesis of silver nanoparticles (Ag-NPs) using microorganisms, or plant extracts has emerged as an alternative approach. The interest in biosynthetic methods for Ag-NPs has number of reasons. They are simple, inexpensive compared to its effectiveness, provide large quantities, harmless and environment friendly. The study revealed the determine an average particle size of silver nanoparticle by dynamic light scattering ZetaSizer which is a technique used for determining the size and distribution profile of *G. mangostana* showing NPs size which was 133.8 nm, this result approves with homogenous distribution and variety size with no agglomerate of resulting nanoparticles, which was clearly observed from the appearance of one peak (Figure 1)

Additionally, TEM image (Figure 2A-2B) demonstrated that the most Ag-NPs were obviously spherical or polygonal in morphological shape, with a size up to 93.50 nm. The color of Ag-NPs aqueous solution was not change indicating the stability of Ag-NPs particles. These results match with the results of ZetaSizer.

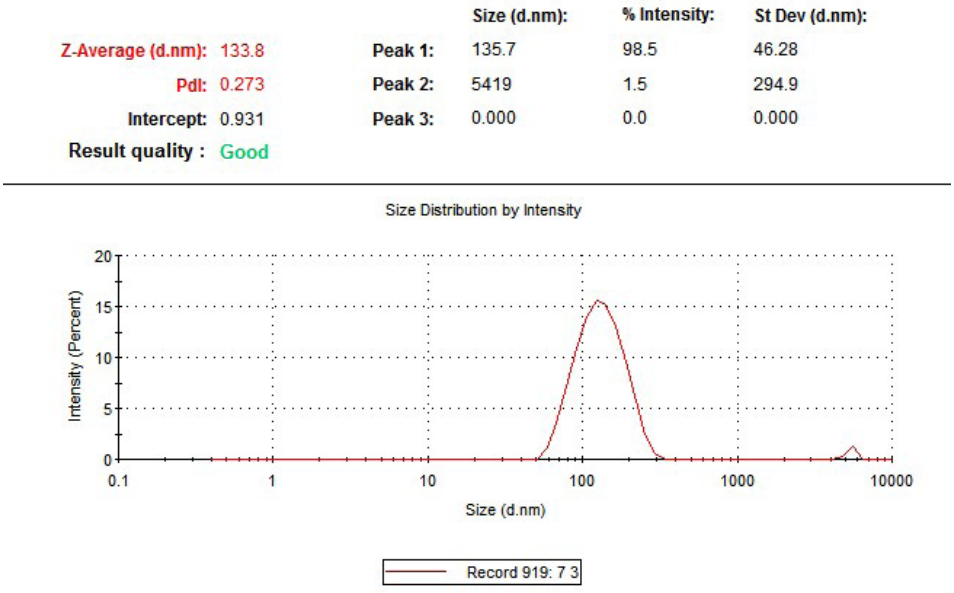

Figure 1. Presents a graph of a zeta sizer for measuring the average size of silver green nanoparticles with *G. mangostana.*

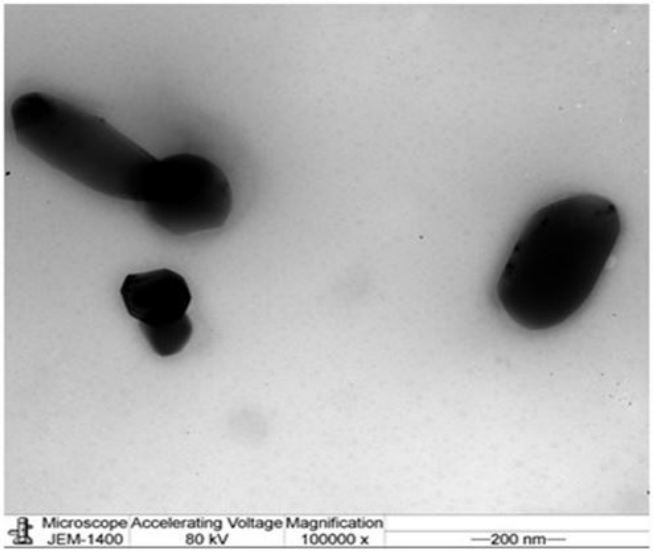

Figure 2. Presents a graph of Transition Electron Microscopy (TEM) image of silver green nanoparticles with G mangostana synthesized (scale bar: 200 nm).

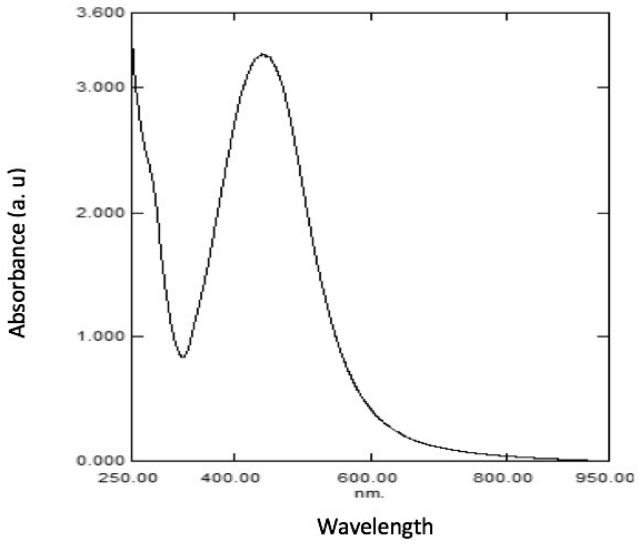

Figure 3. Ag nanoparticles spectrum is observed in the figure characteristic absorption peak of the sample is noted as 400 nm.

Silver green Nanoparticles Ultra violet and visible absorption spectroscopy is the technique by which we measure attenuation of light which passes through a under consideration sample or also after reflection from the sample (Figure 3).

MCF-7 cell line has a epithelial-like morphology which is very similar to mammary epithelium and differentiated in having the ability to process estradiol via cytoplasmic estrogen receptors and capability of forming domes.

As shown in (Figure 4) MCF-7 cell after 24 h were destructed and a slight of morphological changes comparison to control group with healthy cells, after 48 h. Cells started to aggregate.

As shown in (Figure 5) MCF-7 cells after 24 h at 10 µg/mL conc. a change in shape and structure of cells in comparison to control group with healthy cells, however after 48 h. Cells started to have an elongated morphological behavior.

MCF-7 cells after 24 h exposure of 15 µg/mL conc. small colonies started to form with empty space in between cells in comparison to control group with healthy cells, however after 48 h. Cells started to have an outspreaded morphological behavior (Figure 6).

MCF-7 cells after 24 h exposure of 50 µg/mL conc. cells were magnificently destructed and changed in shape in comparison to control group with healthy cells, however after 48 h. Exposure more Destruction & degeneration happened (Figure 7).

MCF-7 cells after 24 h exposure of 70 µg/mL conc. cells showed apoptotic fragmentation which started to occur with massive cell degeneration in comparison to control group with healthy cells, however after 48 h. Exposure cytoplasmic leakage happened due to membrane breakage (Figure 8).

The cytotoxic effects of the silver nanoparticles with MPE on the viability of the Human breast epithelial MCF-7 cells are presented as percent cell viability in (Figure 9A-9B). The MCF-7 cells were exposed to MPENPs at the concentrations of 0, 5, 10, 15, 50 and 70 µg/mL for 24 h & after 48 h, cytotoxicity was determined by MTT assays, that as the concentration of MPE-NPs increased, cytotoxicity was observed in dose-dependent manner.

4 Discussion

Breast cancer is one of the three most common cancers worldwide. Early breast cancer is considered potentially curable. Therapy has progressed substantially over the past years with a reduction in therapy intensity, both for locoregional and systemic therapy; alternative therapy has become a major focus (Rajakannu et al., 2015; Khan et al., 2018).

Human cells are typically 10 µm across. However, the cell parts are much smaller and are in the sub-micron size domain. Even smaller are the proteins with a typical size of just 5 nm, which is comparable with the dimensions of smallest manmade nanoparticles. This simple size comparison gives an idea of using nanoparticles as very small probes that would allow us to spy at the cellular machinery without introducing too much interference (Thirumurugan et al., 2016; Madhavan et al., 2021).

G. mangostana linn belongs to the family of Guttiferae, has numerous properties such as, anti-inflammatory, anti-oxidant and anti-tumor. Green natural products have made and continue to make a vital contribution to the search for new anticancer drugs and to evaluate their anticancer and antioxidant activity *in vitro*. Green Ag-NPs using *G. mangostana* peel extracts are used to increase solubility of green Ag-NPs by more than 10,000-fold and generate targeted delivery systems.

The forms of nanoparticles for *G. mangostana* are polymeric, nanofibers, and nanoemulsions.

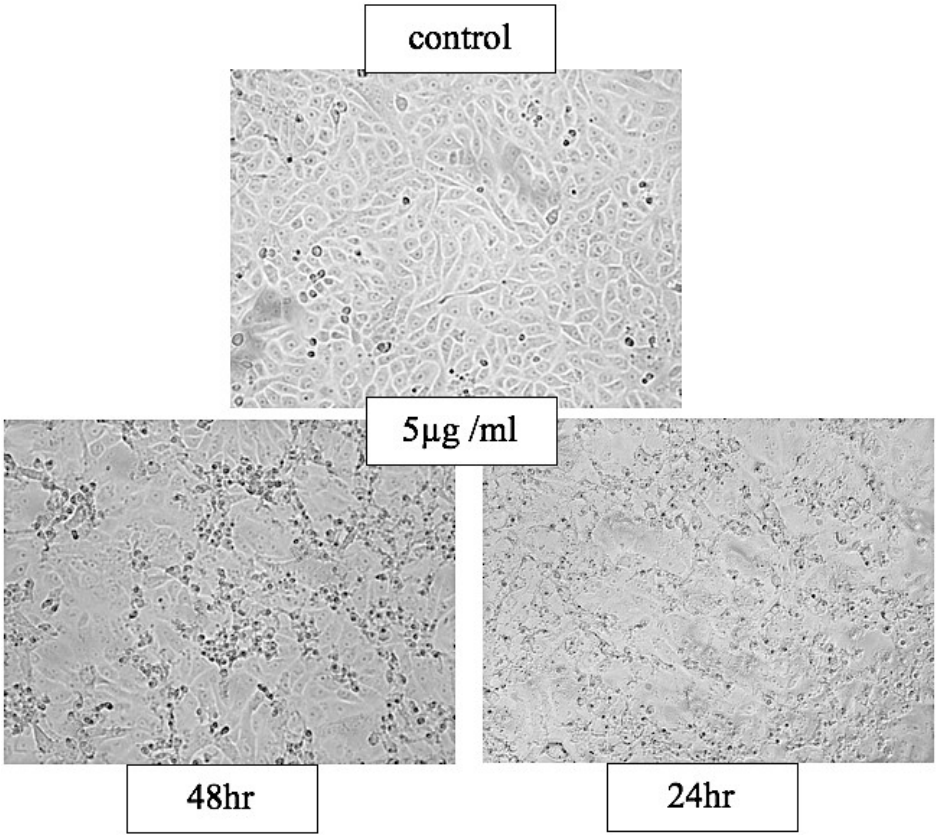

Figure 4. Morphological changes on MCF-7 cells at 5 µg/mL conc.

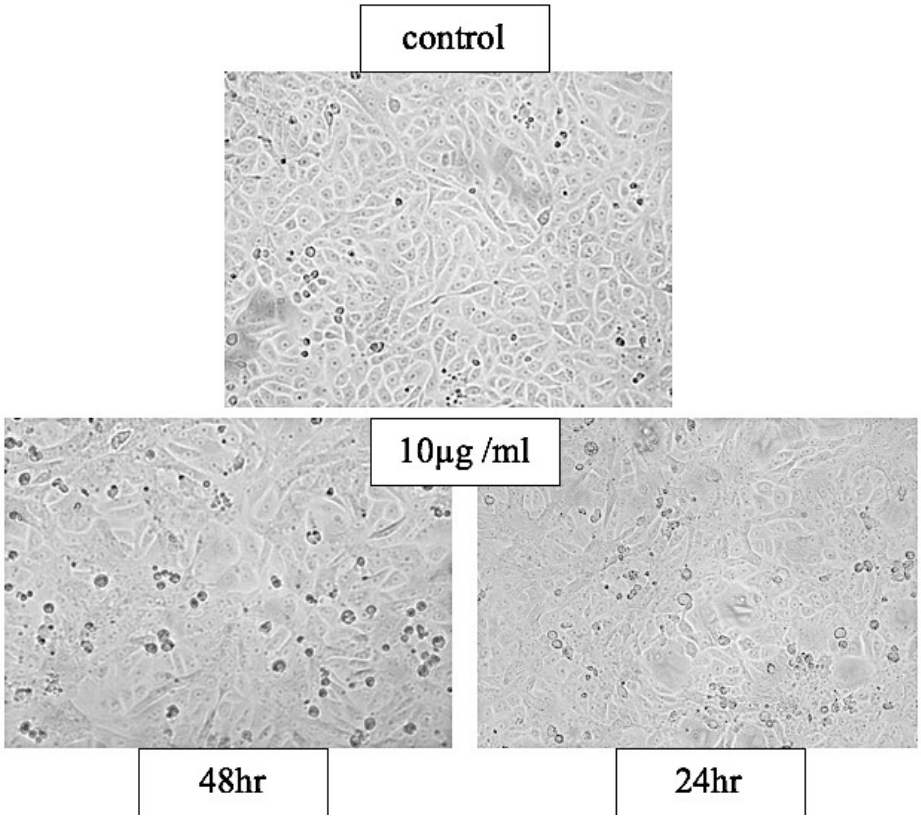

Figure 5. Morphological changes on MCF-7 cells at 10 µg/mL conc.

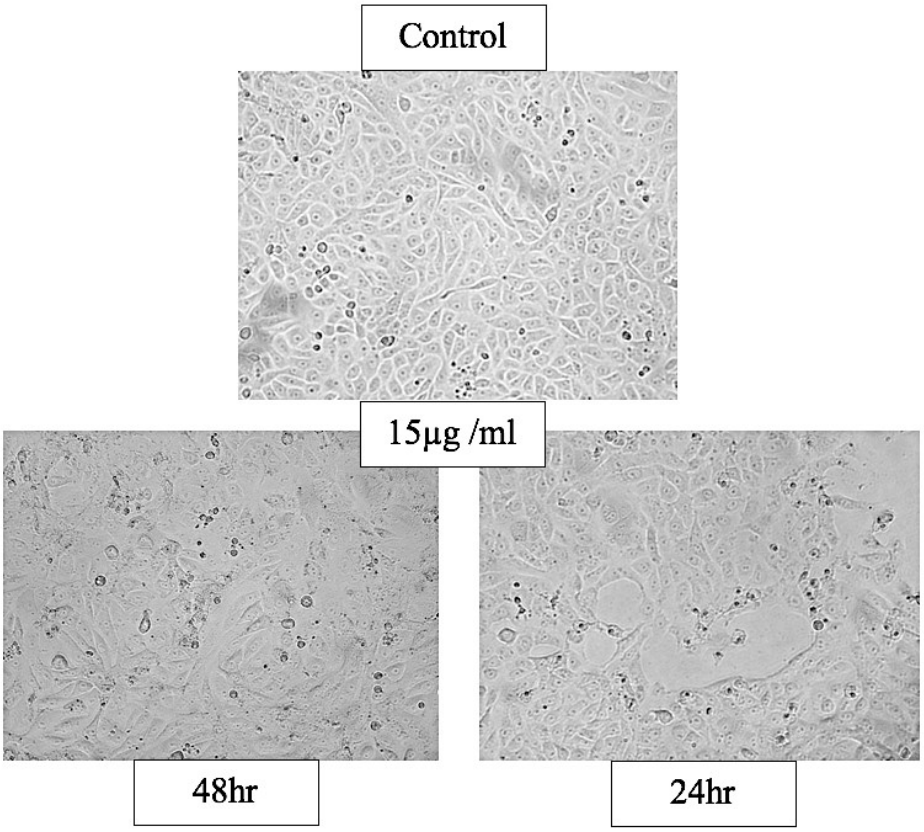

Figure 6. Morphological changes on MCF-7 cells at 15 µg/mL conc.

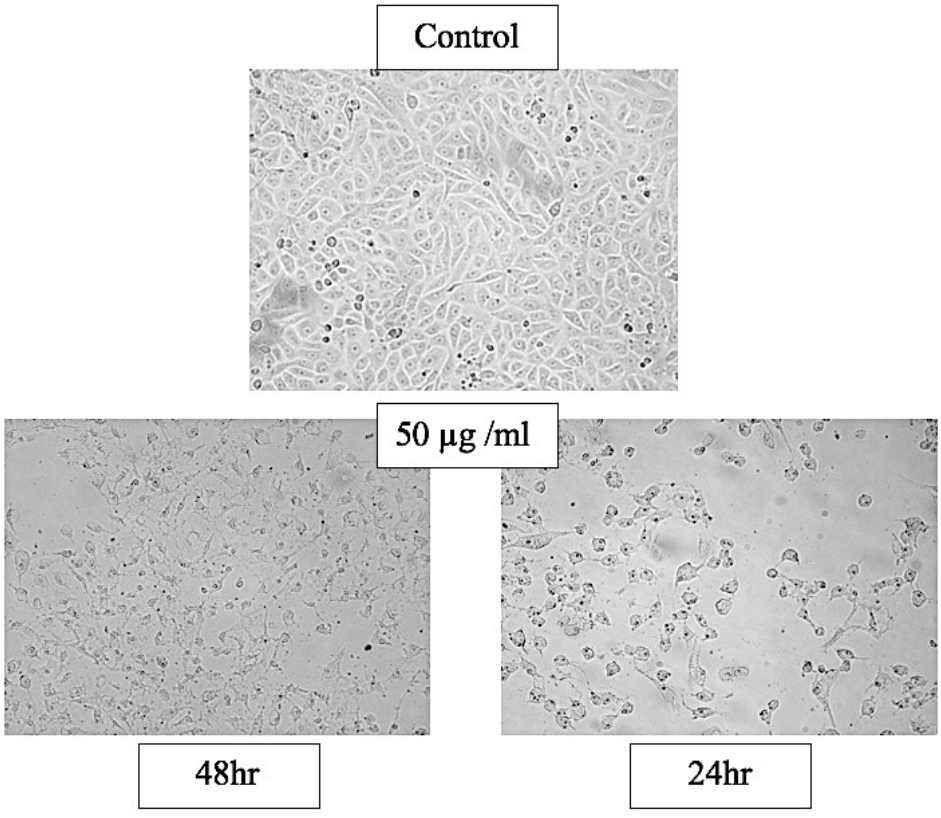

Figure 7. Morphological changes on MCF-7 cells at 50 µg/mL conc.

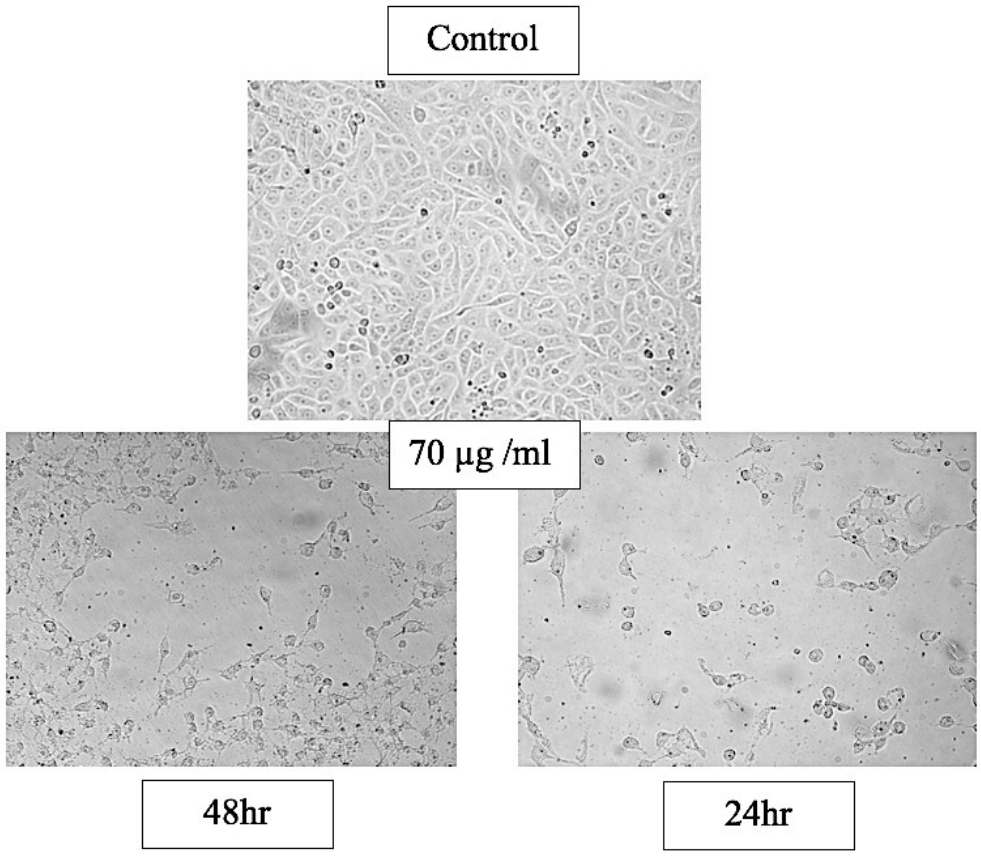

Figure 8. Morphological changes on MCF-7 cells at 70 µg/mL conc.

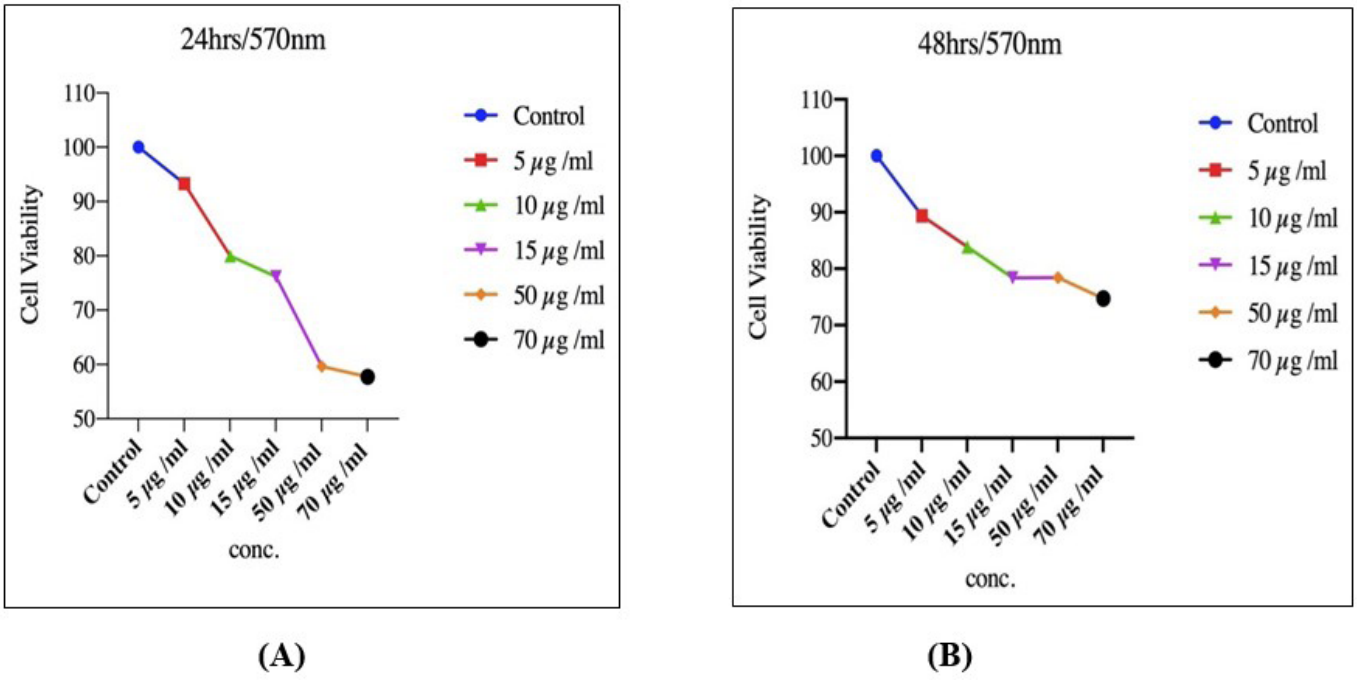

Figure 9: Cell viability curve at 570 nm, after 24hrs (A) & 48hrs (B).

The unique physicochemical physiognomies of metal NPs, such as broad visual properties, and surface functionalization offer new opportunities for cancer therapeutics. The synthesis of silver nanoparticles (AgNPs) has become the thing of powerful research and several methods have been developed to synthesize noble metal NPs, including physical and chemical ones. Early

diagnosis to any disease condition is significant to confirm that early treatment is started and maybe leading to a far better chance of cure. The effectiveness of a therapeutic agent in its ability eliminates tumors and inhibited cell viability without injuring the healthy tissues (Singh et al., 2019; Bhattacharya et al., 2022).

Studies approved that the pericarp extract had anti-proliferative potential against MCF-7 cells by inducing apoptotic cell death. In addition, it induced apoptosis in human breast cancer (SKBR3) cells by investigation of morphological changes and oligonucleosomal DNA fragments (Ahn et al., 2022). Several studies showed as cytotoxic activity of Mangosteen Peel Extract (MPE) against MCF-7 cells designed by using MTT test, and were analyze using Probit analysis to induce IC50. MPE had strong cytotoxic activity on MCF-7 cells with IC_{50} value of 45 µg/mL and morphological changes felt apoptosis induction (Srikar et al., 2016; Balasubramanian et al., 2020; Abate et al., 2022).

In this study we assessed the influence of green Ag-NPs using *G. mangostana* peel extracts as ant proliferative activity against human breast cancer cell line MCF-, it is proved that a probable relevance between antioxidant activity and cancer inhibition of cell growth (Wathoni et al., 2020; Saraswathy et al., 2022).

5 Conclusion

In conclusion, the treatment with green Ag-NPs using *G. mangostana* peel extracts suppressed multiple human breast cancer cell line MCF-7 proliferation by decreasing the creation of cancerous compounds through inhibition of intracellular reactive oxygen species and increases the activity of antioxidant defense system.

Conflict of interest

The authors declare no conflicts of interest.

Availability of data and material

The data used to support the findings of this study are included within the article.

Author contributions

H.M.A., A.F.A., R.A.A. and M.F.E. contributed to study design. A.H.A., N.A.M and F.N.A. contributed to data acquisition. H.M.Y., and M.A.A. organized the database, performed the statistical analysis. All authors revised, improved, read, and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

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