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Original Article

Green synthesis of lutein conjugated copper nanoparticles in treating lung carcinoma

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Abstract

With an estimated 2 million diagnoses and 1.8 million deaths, lung cancer is the primary cause of cancer incidence and mortality worldwide. Because of their special qualities, lutein conjugated nanoparticles (NPs) have gained popularity as cancer therapeutic agents. Using lutein extracted from Broccoli (Stalk and florets), the copper nanoparticles were synthesized and characterized using NTA and SEM. The FLNPs showed significant cytotoxic effects on A459 cell lines, according to the MTT analysis. For PC and FLNP, the IC50 values were 56 and 114 µg/ml, respectively (P<0.05). When compared to the control (no treatment), All three gene members (LGR5, ALDH1, and CD133) shown down regulation (P<0.05) according to the real-time PCR analysis. The results showed that the FLNPs had encouraging cytotoxic effects on lung cancer cell lines.

Keywords: *Lung cancer, Lutein, Copper nanoaprticles, MTT, Real time PCR.*

Introduction

Over the past few decades, a number of research organizations have become interested in the marriage of nutraceutics with nanotechnology. Nutraceuticals are regarded as active ingredients that are prevalent in natural products and have positive health impacts on people. Unfortunately, the inappropriate chemico-physical characteristics of many nutraceutical products limit their applications and, in turn, their health benefits. Many nutraceuticals, for instance, have poor absorption, low stability, high vulnerability to light and oxygen, low water solubility, and the potential to undergo chemical changes after delivery [Abdel-Aal el-SM, 2013]. Given the potential effectiveness of nutraceuticals and their limitations, nanotechnology may be a game-changing development that enhances the positive effects of nutraceuticals on human health and, consequently, their effectiveness in treating a number of illnesses. Nanotechnology may therefore mark a new development in supplemental nutrition [Abdel-Aal el-SM, 2013].

Broccoli as anticancer agent

Often referred to as cruciferous vegetables (Cruciferae), broccoli (Brassica oleracea var. Italica) is a herbaceous plant of the Brassicaceae family. Its high nutritional value and low energy content are attributed to its fiber, potassium, folate, and vitamin C and K contents [Gasper A.V., 2005]. Broccoli contains sulforaphane, a substance that is produced when myrosinase hydrolyzes glucoraphanin. The nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that positively controls genes linked to the synthesis of antioxidant proteins essential for counteracting oxidative damage, is strongly induced by this glucosinolate. Recently, Nrf2 has been linked to changes in central metabolic pathways [Hayes J.D., 2014]. Numerous biological characteristics of sulforaphane have been demonstrated to improve human health. In a number of cancer types, including colon, stomach, bladder, prostate, breast, skin, and lung cancers, it has been identified as a chemopreventive and protective agent [Yang L., 2016]. Millions of people die from cancer every year, making it one of the major causes of death globally.

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Because conventional medicines like chemotherapy, radiation therapy, and surgery are frequently non-specific, they can cause serious adverse effects by destroying both healthy tissues and malignant cells. For example, chemotherapy drugs are unable to distinguish between healthy and cancerous cells, which results in systemic toxicity, immunological suppression, and a lower standard of living for patients (Lau et al., 2004). Furthermore, a significant obstacle to the long-term treatment of cancer is the emergence of drug resistance in tumors. These difficulties highlight the pressing need for cancer treatment strategies that are more accurate, efficient, and less harmful.

Nanotechnology has emerged as a potential remedy for the problems with conventional cancer treatments in recent years (Chen S. et al., 2023). Nanotechnology presents previously unheard-of possibilities to enhance cancer detection, therapy, and monitoring. Nanotechnology is the control and manipulation of materials at the atomic or molecular level, usually involving materials with diameters of 1–100 nm. Researchers have created new therapeutic and diagnostic tools that offer better targeting, lower toxicity, and increased therapeutic efficacy in the clinical setting by utilizing the distinct physical, chemical, and biological characteristics of nanomaterials (Gong et al., 2019).

Nanoparticles as drug carriers

One of the most promising technologies in the field of drug delivery, especially for the treatment of cancer, is nanoparticles (NPs). The exact and targeted distribution of chemotherapeutic medicines is made possible by the special properties of these nanoparticles, which include liposomes, dendrimers, metallic nanoparticles (such gold and silver nanoparticles), polymeric nanoparticles, and others. The ability of NPs to encapsulate medications and deliver them straight to tumor cells is their main advantage as drug carriers, guaranteeing a greater concentration of the therapeutic agents at the intended location (Chen W. et al., 2023). By doing this, the drug's effectiveness is maximized and the systemic toxicity that is frequently linked to traditional chemotherapy is greatly decreased (Aftab et al., 2018).

Utilizing the increased permeability and retention (EPR) effect is one of the main reasons why nanoparticles are so successful at destroying tumor cells. Unusual vasculature allows for accessible penetration of even huge molecules and retention of those large molecules due to an insufficient immune system built around them, which is caused by aberrant angiogenesis brought on by malignant cells. Nanoparticles' capacity to penetrate enables them to naturally collect in the tumor microenvironment, and their capacity to stay there because of the tumor's inadequate lymphatic drainage results in extended medication exposure at the tumor site (Li et al., 2014).

Copper nanoparticles in cancer therapy

Because of their special qualities and complementary effects, metal-based nanoparticles have shown promise in a number of therapeutic fields. In this context, copper nanoparticles have drawn particular interest as promising cancer treatment possibilities. According to Shen et al. (2022), these nanoparticles have exceptional qualities such as a high surface area to volume ratio, outstanding compatibility with living things, and the capacity to produce reactive oxygen species (ROS) in the presence of an acidic tumor microenvironment. The ability of copper nanoparticles to selectively target cancer cells while protecting healthy cells is one of their key benefits in cancer treatment. By functionalizing the nanoparticles' surface with certain ligands or antibodies that can identify and attach to cancer cells, the targeting strategy can be accomplished. By delivering treatment medicines directly to the tumor, the targeting mechanism reduces the likelihood of off-target consequences (Shen et al. 2022).

Lutein

A ubiquitous yellow-orange pigment in plants, lutein belongs to the xanthophyll family of carotenoids. Yellow-colored foods like corn and egg yolks, as well as dark leafy greens like spinach and kale, are dietary sources of lutein. According to Granado (2003), lutein contains anti-inflammatory, anti-oxidant, and anti-cancer qualities. Thus, lutein supplementation may help avoid inflammatory conditions brought on by oxidative stress, such as cardiovascular illnesses, diabetic retinopathy, and neurodegenerative disorders [Kavalappa, Y.P, 2020].

Here, however, we present the copper nanoparticles loaded with lutein and their possible anti-bacterial, anti-cancer, and antioxidant properties. In order to accomplish our goal, we suggested this study because research has indicated that lutein nanoparticles are more bioavailable than free lutein. Our work uses the broccoli-based nanoparticles and conjugated with lutein so as to enhance the biomedical properties. In this objective, we evaluated the antiproliferative capacity of the green-synthesized copper nanoparticles from *Broccoli* to examine the cytotoxic effects on A549 human lung cancer cells.

Methods

Brassica oleracea var. italic was washed thoroughly with running tap water and then with distilled water to get rid of dust and unwanted dirt particles. Florets and Stalks were sun dried and pulverized into fine powder and filtered using filter papers. The powders were boiled separately and the filtrate obtained was used for the green synthesis.

Lutein extraction

With a few minor adjustments, lutein was extracted using the solvent method described by N.M Sachindra and Mahendrekar (2005). In a nutshell, the extraction process involved mixing 1gm of powdered material with 200mL of acetone and petroleum ether (50% v/v) for 24 hours at 40°C in a shaking water bath. To separate the phases and get rid of any petroleum ether residue, a 0.1% NaCl solution was added to the mixture. After that, the mixture was centrifuged for 15 minutes at 8000 rpm and 25°C. In a lyophilizer, the resulting supernatant was freeze-dried. Before analysis, the dried samples were stored at 20°C.

Green synthesis

About 50ml of 3mM Copper sulphate solution was mixed with 50ml of lutein fraction (1:5 ratio). Green synthesis was carried with four samples. The boiled extract

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from both stalk (SNP) and florets (FNP) were also used for green synthesis. Both Stalk (SLNP) and Florets (FLNP) lutein extracted was studied separately. The contents are mixed thoroughly and kept on magnetic stirrer. Colour change was confirmed as nanoparticle formation. The contents are centrifuged at about 8000rpm for 15min. The pellet obtained was then dried in hot air oven at 80°C.

Dynamic light scattering (DLS) and Characterization: The surface morphology and atomic ratio of the CuNPs were determined using FESEM-EDX at an accelerating voltage of 15KV (SEM; PhilipsXL30ESEM). Using a Horiba SZ-100 analyzer, the hydrodynamic size (Z average), surface charge (zeta potential), and polydispersity index (PDI) of the ecologically produced CuNPs were screened using the DLS method in Kyoto, Japan. At a 90° scattering angle and 210kCPS medium count rate, the particle size was analyzed.

Samples used in the study: FNP: Florets NPs; **SNP:** Stalk NPs; **L:** Lutein NPs; **FLNP:** FNPs conjugated with Lutein; **SLNP:** SNPs conjugated with Lutein

Cell culture and treatment: In monolayer cultures, the cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 media supplemented with 10% fetal bovine serum (FBS), 100U/mL penicillin, 100mg/mL streptomycin, and 2mM glutamine. The cells were then incubated at 37°C in a humidified atmosphere with 5% CO_2 in the air.

Cell Viability Assay: In order to study the cytotoxic potential of the synthesized NPs (FNP, SNP, L, FLNP and SLNP), MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed as per the earlier described protocol with slight modifications (Ahmad et al., 2021). Briefly, 5×10^3 A549 cells/well were seeded in a 96-well plate with medium and allowed to adhere in a humidified atmosphere. Normal cells (3T3 fibroblasts were also used to study the effect on the normal cells in parallel. Cells were treated with different concentrations of NPs (20, 40, 80, 120, 160 and 200µg/ml) and further incubated for 24hr under standard conditions. MTT dye (10µl; 5 mg/ml) was added to all the wells and further incubated for 4hr (37 °C). Standard drug Gefitinib was used as a positive control throughout the study. The MTT assay for percentage inhibition was done. IC_{50} values were calculated using GraphPad Prism software. % cell inhibition= 1-{ (AT-AB) / (AC-AB) } x100. Where, AT= OD OF treated sample; AB= OD of blank; AC=OD of control

LDH Assay

LDH reagent (HiMedia, India) was used to calculate the amount of LDH that leaks from cells after membrane disruption (Kumar G, 2019). And then, they were treated with 1/2MIC, MIC and 2MICµg/ml concentrations of the FNP, FLNP and incubated for 72hr respectively. Gefitinib (2MIC, 112µg/ml) was used as positive control. Following a 30-minute dark incubation period at room temperature, the plates were all measured at 340 nm using an ELISA plate reader (Genetix, India).

RNA extraction and cDNA synthesis

Using an RNeasy mini kit (Qiagen, Iraq), total RNA was extracted from both the control and treated cell lines (MIC) in accordance with the manufacturer's instructions. This was done using a HiMedia® Reverse Transcription Kit (HiMedia, India). Reverse transcription was carried out using 14µl of cDNA produced by incubating the mixture (1µl of reverse transcriptase, 4µl of RT buffer, and 1 µl of reverse transcription primer mix) 42°C for 15min. Real-time PCR analysis of gene expression was performed using the reaction products.

qPCR of cytokine associated genes

Following reverse transcription-PCR, real-time PCR was performed utilizing the cDNA products. The manufacturer's instructions were followed while using a SYBR Green PCR Kit (HiMedia, India) using a two-stage cycling strategy that included denaturation at 94°C and a combined annealing/extension step based on the primer Tm value. Real-time PCR was performed under the following conditions: initial denaturation at 94°C for 4min, 40 cycles of 94°C for 25s and annealing at 57°C for 10s. Each gene's expression was normalized to that of β -actin. We evaluated the genes for LGR5, ALDH1 and CD133.

Table 1: lists the primer and probe sequences utilized in this real-time PCR. Real-time quantitative PCR experiments are can be used to examine the relative changes in gene expression using the $2^{-\Delta\Delta CT}$ method.

Gene	Primer sequence (5′–3′)	Base pairs	Tm	GC%	Product size (bp)	Reference
LGR5	GCAAACCTACGTCTGGACAA	21	56.46	54.5	250	[Udoh K, 2019]
	TGATGCTGGAGCTGGTAAAG	21	58.6	55		
ALDH1	GCACGCCAGACTTACCTGTC	21	62.3	55	280	This study
	CCACTCACTGAATCATGCCA	21	63	56.4		
CD133	AGTGGCATCGTGCAAACCTG	20	61.4	56	345	[Udoh K, 2019]
	CTCCGAATCCATTCGACGATAGTA	20	62.3	52		
β-actin	CGCACCACTGGCATTGTCAT	21	68	58	350	This study
	TCCAAGGCGACGTAGCAGAG	21	68	54		

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Statistics Analysis

SPSS (faculty version) was used for the data analysis. Standard metrics like mean and standard deviation (SD) values were used to display the data. A P-value of less than 0.05 was considered statistically significant.

Results

Nanoparticle synthesis

Colour change to dark green was considered formation of nano particles. The particles were centrifuged and the dried particles were used for characterization studies. UV spectra showed a peak at 245nm which depicts the formation of copper nanoparticles as reported by previous findings [Sivaraj R, 2014]. The green synthesis of CuNPs (GCuNPs) using *brocoli* (florets and stalks) showed changes of color in the aqueous solution from light yellow to reddish-brown in case of florets and light pink to reddish brown in case of stalks. From our findings, we found a peak value of 240 and 250nm for florets (F) and stalks (S) respectively.

NTA analysis

The NTA images showed most of the synthesized nanoparticles are having an average size diameter in the range of 70 to 35nm which was calculated on the basis of Brownian motion of particles. GCuNPs with florets showed an average size of 43nm. On the other hand, GCuNPs with stalks showed an average size of 70nm. The size and shape of the produced AgNPs were also investigated using scanning electron microscopy.

Structural Characterization of Lutein in the nanoparticles by FTIR

FTIR verified that the lutein extract was stable in the NPs. Figure displays the FTIR spectra of the lutein NPs from the stalk and florets as well as the lutein removed from the florets in the preceding stage. They provide details on the lutein extract's molecular structures in the lutein nanoparticles. At 2921cm^{-1} and 2856cm^{-1}, the distinctive absorption bands of the lutein reference standard emerged, signifying the symmetric and asymmetric stretching vibrations of CH_2 and CH_3. The adsorption band located at 3432cm^{-1} is attributed to hydrogen bonding between molecules. Similarities in the functional group environment are suggested by the frequencies, which are closer to those obtained with the lutein isolated from the lutein NPs. Thus, at 0 weeks of storage, the FTIR measurements confirm the molecular structure of the lutein extract in the lutein NPs.

SEM:

The shape of the nanoparticles was nearly spherical, with less evidence of agglomeration. Previous studies confirmed CuNPs' spherical shape. The average particle size determination using ImageJ software showed that the average particle size was in the range of 35 -78nm. The particle size distribution for CuO NPs obtained in this study agreed with previous studies.

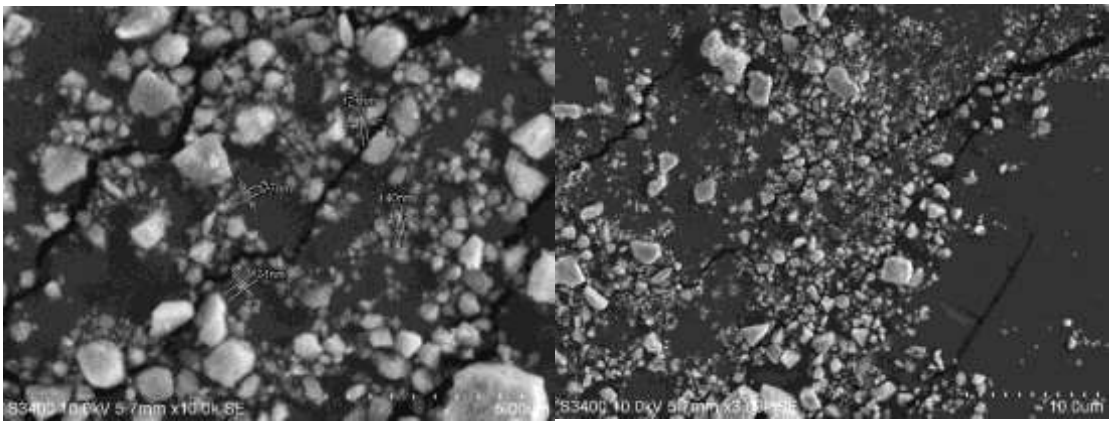

Figure 1: SEM images of the green synthesized nanoaprticles (FLNP).

Cell viability assay: The antiproliferative activity of the screened NPs on A549 cell lines and normal cell lines (3T3) was assayed by the colorimetric MTT assay. We found, the flower NPs (FNP) and flower nanoparticles conjugated with lutein (FLNP) exhibited strong anti-proliferative activity. The activity was found to be dose dependant ($P<0.05$). The percent inhibition was found to be 100% at 200µg/ml and the FLNP showed 100% inhibition at 400µg/ml. FNP showed 90% inhibition at similar concentration ($P<0.05$). This confirms the possible cytotoxic activity against the cancer cells. IC50 values were found to be 56 and 114µg/ml respectively for PC and FLNP ($P<0.05$).

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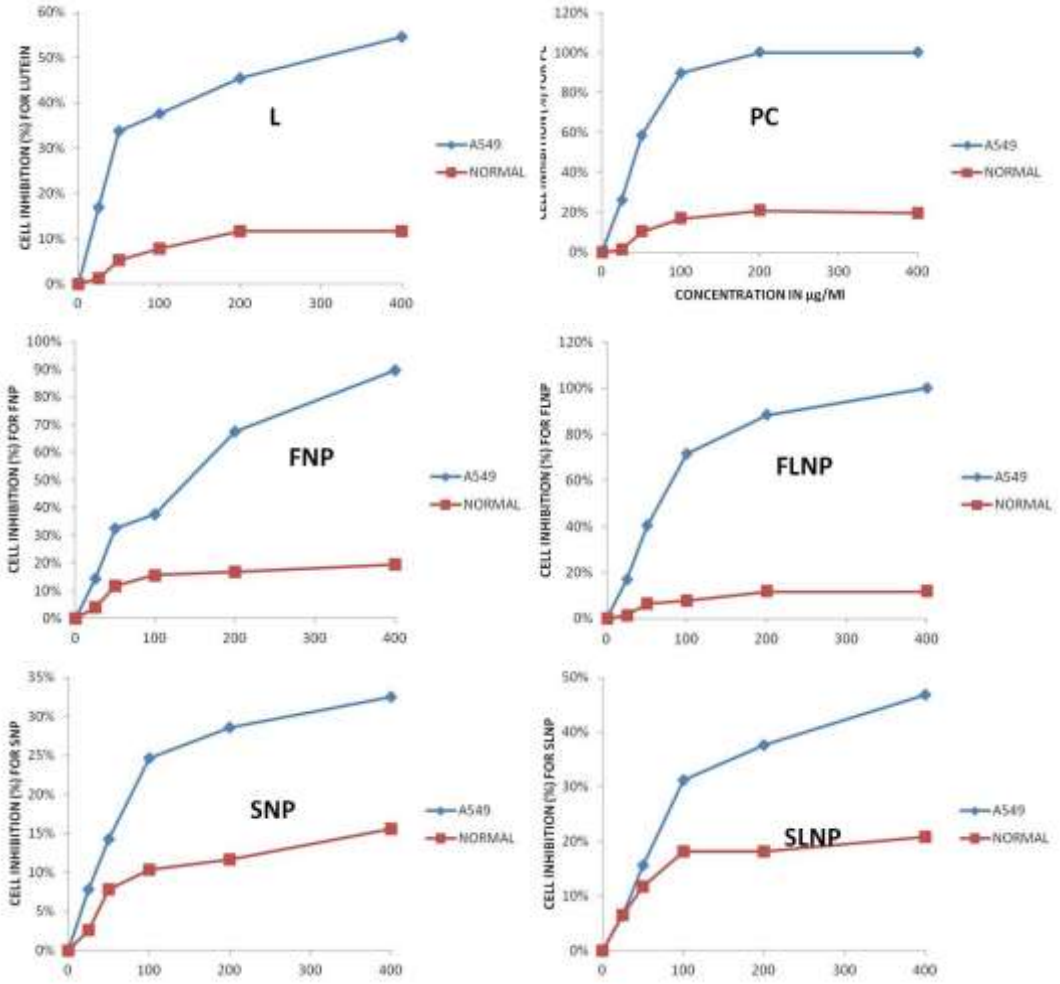

Figure 2: Cell inhibition by viability assays. Synthesized NPs on A549 lung cancer cells and 3T3 fibroblasts. Following treatment for 72hr, cell viability was determined with the MTT assay.

LDH assay: From our study, we found both FNP and FLNP were capable to damage the cells and stop the proliferation. The amount of LDH is directly proportional to the damage to the cells. LDH release was found to be 18 and 31% at MIC concentration. This was highly significant when compared to positive control (38) ($p<0.05$).

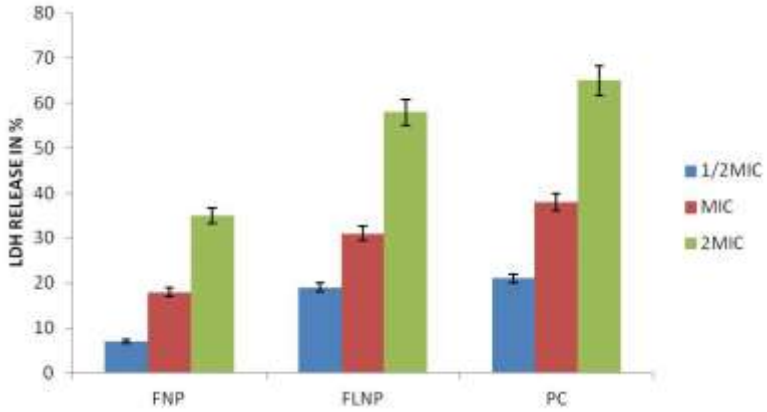

Figure 3: LDH assay. Histogram showing the LDH release in % from the cells with treatment. Control OD value was found to be 0.12.

Real time PCR: From the data obtained, we found the gene members were down regulated upon treatment with NPs. All the three gene members showed down regulation ($P<0.05$). LGR5 gene expression was significantly down-regulated to 0.65 times from 1 (control) throughout the study. Control expression was considered 1 or 100%. ALDH1 gene expression was significantly down-regulated to 0.88 times from 1 (control) throughout the study. Control expression was considered 1 or 100%. CD133 gene expression was significantly down-regulated to 0.56 times from 1 (control) throughout the study. Control expression was considered 1 or 100%.

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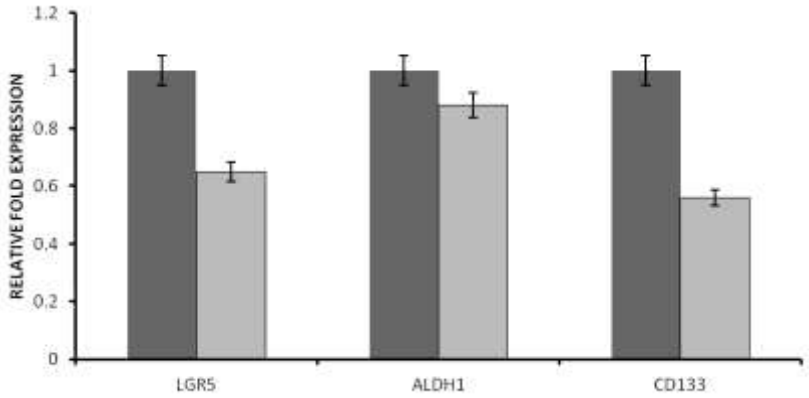

Figure 4: Relative fold expression of the LGR5, ALDH1 and CD133 among the subjects and control. Control expression is considered 1 or 100%. Beta actin was used as housekeeping gene ($p<0.05$).

Discussion

Lutein conjugated to nanoparticles improves its stability, targeted delivery, and bioavailability, which greatly increases its anticancer actions against cancer cells [Saini, R.K, 2022]. The drawbacks of free lutein, including its low solubility and poor chemical stability, are addressed by this sophisticated delivery system [Tan, B.L, 2019]. Through a variety of methods, many of which are more effective than those of free lutein, lutein nanoparticles fight cancer cells. When lutein concentrations are high, it transforms from an antioxidant to a pro-oxidant, raising ROS levels in cancer cells in particular [Maiani, G, 2009]. Increased oxidative stress has the potential to harm cell constituents and trigger apoptosis, or programmed cell death. Lutein supplied by nanoparticles more efficiently induces apoptosis in a variety of cancer cells, including cervical and breast cancer lines [Namitha, K.K, 2010].

The colorimetric MTT assay was used to evaluate the selected NPs' antiproliferative effects on A549 and normal cell lines (3T3). We discovered that there was significant anti-proliferative action in both flower nanoparticles (FNP) and flower nanoparticles conjugated with lutein (FLNP). It was discovered that the action was dose dependent ($P<0.05$). At 200µg/ml, the percentage inhibition was 100%, and at 400µg/ml, the FLNP displayed 100% inhibition.

According to research on non-small-cell lung cancer (NSCLC) cells, lutein-loaded nanoparticles may be more potent than free lutein because of their lower inhibitory concentration (IC50). For instance, it has been observed that certain polymeric nanocarriers can enhance the antiproliferative action of lutein by a magnitude greater than two [Majumdar D, 2014]. By blocking the phosphoinositide 3 kinase (PI3K)/protein kinase B (PKB) signaling pathway, lutein therapy has been shown to promote apoptosis in A549 human non-small-cell lung cancer cells [Zhang WL, 2018].

Our LDH analysis revealed that both FNP and FLNP had the ability to harm cells and halt their growth. Comparing this to positive control (38) revealed that it was highly significant ($p<0.05$).

In vitro and in vivo, luteolin caused prostate cancer cells to proliferate less and undergo apoptosis. It enhanced cisplatin's effectiveness against stomach cancer cells. Lutein also prevented the formation of tumors against breast cancer cell lines (MCF-7/6 and MDA-MB231-1833) in an animal model. In a different study, luteolin dramatically decreased the number of tumors per rat and the incidence of colon cancer (Manju V, 2007).

We discovered from our real time PCR data that the gene members were down-regulated after being treated with NPs. Throughout the investigation, there was a considerable down-regulation of LGR5 gene expression, which was 0.65 times lower than the control value of 1. A control expression of 1 or 100% was used. Throughout the investigation, the expression of the ALDH1 gene was considerably down-regulated, decreasing to 0.88 times that of the control. A control expression of 1 or 100% was used. Throughout the investigation, there was a considerable down-regulation of CD133 gene expression, which was 0.56 times lower than the control value of 1. A control expression of 1 or 100% was used.

LGR5 is downregulated in cancer cells, according to several studies, and this is frequently a sign of treatment resistance. Through targeted medication delivery, gene silencing, and other therapeutic approaches, nanoparticles are a key tool for researching and influencing this process. It has been demonstrated that LGR5 downregulation activates the MET-STAT3 pathway, giving LGR5-negative colorectal cancer cells a survival advantage and making them more resistant to therapy (Posey TA, 2023).

Studies have delivered small interfering RNA (siRNA) that selectively targets ALDH1A1 using nanoparticles, such as nanoliposomal carriers. This method effectively shut down ALDH1A1 in ovarian cancer models, sensitized chemotherapy-resistant cells, and markedly slowed tumor development. A combination of ALDH1A1-siRNA and either cisplatin or docetaxel was administered via nanoparticles in ovarian cancer research. When compared to either medication alone, this combination therapy had a synergistic effect that considerably decreased tumor weight [Abu-Serie MM, 2024].

Conclusion

We found both FNP and FLNP were good at inhibiting the cell division capacity among the cancer lines A549. We found FLNP to be more potent than the FNP, which confirms that our conjugation of the FNPs with Lutein NPs enhanced the anticancer activity of the NPs ($P<0.05$). Due to its potential to improve lutein's effectiveness and targeted distribution, lutein conjugated

nanoparticles are becoming more and more important in cancer research as a possible therapeutic and preventative option. Researchers can increase lutein's solubility, stability, and bioavailability by encapsulating it in nanoparticles. This allows for tailored administration to cancer cells while reducing off-target effects. This strategy makes use of lutein's natural anti-cancer and antioxidant qualities, which may strengthen its therapeutic effects on cancer cells. Although lutein, a carotenoid, has anti-cancer and antioxidant qualities, its efficacy is limited by its low solubility and bioavailability. Lutein's solubility, stability, and capacity to penetrate cancer cells are all enhanced when it is conjugated with nanoparticles (such as PLGA or PLGA-PEG-biotin). By boosting the concentration of lutein at the tumor site through targeted delivery with nanoparticles (such as biotin-decorated nanoparticles), its therapeutic efficacy can be increased while causing less damage to healthy cells.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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