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Biogenic synthesis of silver nanoparticles from *Hylocereus undatus* peel waste: exploring EGFR inhibition for targeted therapy of cervical and breast carcinomas

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Abstract

Background Cancer is one of the leading causes of death worldwide, with breast and cervical cancers being the most common among women. Over 100,000 new cases of breast cancer and 510,000 new cases of cervical cancer are diagnosed annually. This study aimed to develop and evaluate an eco-friendly, low-cost method to synthesize silver nanoparticles using *Hylocereus undatus* (dragon fruit) peel extract for their anticancer activity.

Results Silver nanoparticles loaded with *Hylocereus undatus* fruit peel extract were successfully developed by a green synthesis technique and were optimized by UV–vis spectroscopy. The nanoparticles had an average size of 71.66 nm, a polydispersity index of 0.3754, and a zeta potential of -38.52 , with a spherical shape and 79.5% silver content. Their maximum absorbance was at 448 nm. Further, in vitro anticancer activity via MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay was evaluated and the synthesized nanoparticles displayed IC_{50} values at 23.51 $\mu\text{g/ml}$ and 23.66 $\mu\text{g/ml}$ against Hela and MDA MB 231 cell lines, respectively. Cytocompatibility studies showed high cell viability ($\geq 95\%$) in L929 mouse fibroblast cells, indicating low toxicity. In silico analyses, including network pharmacology and molecular docking, identified kaempferol and quercetin as key anticancer compounds, with epidermal growth factor receptor (EGFR) (PDB ID: 1M17) being the most significant protein target. Docking studies performed by using the Glide module of Schrodinger's software displayed that kaempferol and quercetin had higher binding affinities for EGFR as compared to the standard drug erlotinib, with MET 769 being a crucial binding site.

Conclusion Thus, the outcomes suggest that synthesized silver nanoparticles loaded with *Hylocereus undatus* fruit peel extract could be a potential and promising drug carrier aiding in cancer treatment.

Keywords Silver nanoparticles, *Hylocereus undatus*, Anticancer, Network pharmacology, Molecular docking, EGFR, 1M17, MET 769

Background

Cancer remains a leading global cause of mortality, with projections from GLOBOCAN indicating a substantial increase in cancer cases in India, reaching an estimated 2.08 million by 2040, a 57.5% rise from 2020 statistics [1]. GLOBOCAN 2022 states that among women, breast and cervical cancers are most commonly diagnosed, with 2.3 million new cases and 665,000 deaths owing to breast cancer, and around 660,000 new cases and 350,000

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deaths owing to cervical cancer [2]. Despite extensive research, cancer treatment remains unsatisfactory due to the unique characteristics of cancer cells, including uncontrolled proliferation, invasiveness, metastasis, and dedifferentiation, which complicate targeted treatment. Chemotherapy often results in significant toxicity and adverse side effects due to the use of synthetic drugs, driving interest in natural origin drugs for cancer treatment [2–7]. Current research gaps include the lack of detailed optimization studies for synthesis parameters such as pH, temperature, and reaction time specific to dragon fruit peels, which are crucial for achieving optimal silver nanoparticle (AgNP) characteristics. Additionally, extensive studies are needed to evaluate the biocompatibility and toxicity profiles of these nanoparticles, ensuring their safety for medical use. Moreover, mechanistic insights into how AgNPs synthesized from *Hylocereus undatus* (*H. undatus*) peels exert anticancer effects, particularly through pathways like epidermal growth factor receptor (EGFR) inhibition, are poorly understood. Comparative efficacy studies against AgNPs from other plant sources are also scarce but essential to determine their relative effectiveness and potential advantages. There has been growing global interest in the importance of bioactive compounds from natural origin, which are found to be less toxic compared to conventional chemotherapeutic drugs. Various plant-based drugs are in use for cancer treatment, including vinca alkaloids, epipodophyllotoxins, taxanes, and camptothecin derivatives. Additionally, encapsulated nanomedicine studies have explored the potential of natural drugs such as camptothecin, curcumin, quercetin, and *Emblica officinalis* for the treatment of various cancer cell lines. Integrating phytoconstituents to metal nanoparticles has proven to be a promising approach, enhancing their bioavailability in cancer treatment [7–9]. *H. undatus*, or dragon fruit, is employed in the current study for the synthesis of AgNPs due to its abundant peel waste, rich phytochemical composition, underexplored potential in nanotechnology, biomedical promise, and economic feasibility. Among its diverse biological activities, it has also demonstrated potent anticancer effects [8, 10, 11]. Recent advancements in nanoscience and nanotechnology have unveiled the significance of plants in the bio and green synthesis of nanoparticles, garnering considerable interest. Green-synthesized silver nanoparticles combat cancer by halting cell cycle progression in carcinoma cells. However, in aqueous environments, silver nanoparticles' inertness diminishes, raising cell-specific cytotoxicity concerns, which, if addressed, could enhance their potential for targeted chemotherapy. Recent literature also suggests transforming food waste into valuable nanomaterials, offering a sustainable alternative for

nanoparticle production [10–15]. Thus, the prime aim of this work is to utilize biological waste from *H. undatus* to synthesize silver nanoparticles via a sustainable approach for anticancer therapy, and elucidating their mechanisms of action in EGFR inhibition, ultimately exploring their potential for targeted therapy of cervical and breast carcinomas.

Materials

Chemicals were procured from Sigma-Aldrich and SD Fine, India. The fresh *H. undatus* fruits were collected from the local market in Belagavi, Karnataka, India, and authenticated by a botanist where the fruit was identified and authenticated as per morphological characteristics by Dr. Ajit Lingayat at the institute's herbarium at Shri BMK Ayurvedic Mahavidyalaya, Belagavi, Karnataka.

Methods

Preparation of dried *H. undatus* fruit peels powder

The collected fruits were washed thoroughly with distilled water, the fruit peels were separated and kept in the sunlight for five days. Further, the dried peels were powdered thoroughly using a kitchen blender (Inalsa Jazz 550 V Mixer Grinder) and stored in a tightly closed container at 4 °C until future use (Fig. 1).

Preparation of nanoparticles (NPs) loaded with *H. undatus* fruit peel extract

An aqueous extract for NPs synthesis was prepared by adding 5 g of peel powder in 300 ml of deionized water, stirred at 60 rpm for 30 min using a digital magnetic stirrer (IKA C-MAG HS 7), filtered by using Whatman filter paper, and stored at 4 °C for further use (Fig. 1). The silver nitrate solution was prepared by adding 169.9 mg of silver nitrate into an ambered-colored bottle containing 1000 ml of deionized water and sonicated for 10 min on a sonicator (Zhart, India). Further, the nanoparticles were prepared by adding 10 ml extract to a round bottomed flask containing 90 ml of 1 mM AgNO₃ and heated at 80 °C up till a color change was observed (4 h) with constant stirring. The solution was subjected to centrifugation at 14,000 rpm for 15 min on high-speed refrigerated centrifuge machine (Kubota 7000/230 V), while the supernatant was separated and centrifuged thrice by the same process. The nanoparticles were obtained which were dried at room temperature and stored for further use (Fig. 2) [15, 16].

Optimization of NPs

The optimization of the NPs was performed to evaluate the optimum conditions for the synthesis of silver nanoparticles. Effects of various parameters such as temperature (4 °C, 28 °C, 60 °C, 80 °C), time of reaction

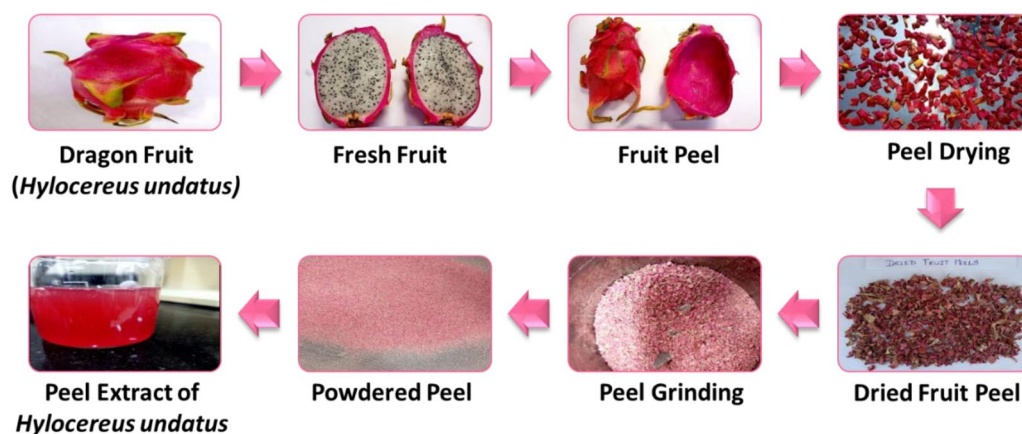


Fig. 1 Process of preparation of *Hylocereus undatus* fruit peel aqueous extract

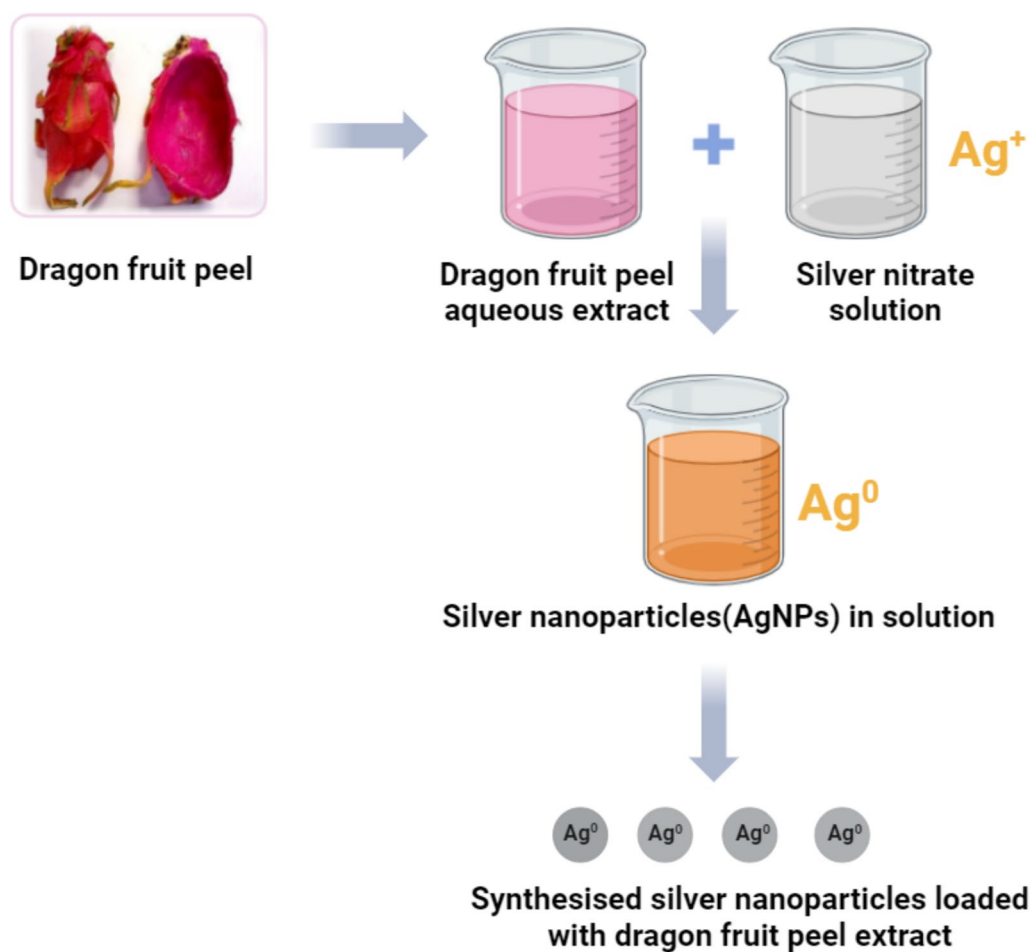


Fig. 2 Synthesis of silver nanoparticles loaded with aqueous extract of dragon fruit peel

(2 h, 4 h, 6 h, 24 h), pH (6, 8, 9, 12), concentration of AgNO_3 (1 mM, 2 mM, 4 mM, 6 mM), and amount of extract (3 ml, 10 ml, 15 ml, 20 ml) were employed for

synthesizing the NPs. 0.1 M sodium hydroxide and 0.1 M hydrochloric acid were used for adjusting the pH of the sample [17–19].

Characterization of NPs

UV-Visible spectroscopy

The UV investigation aimed to confirm the presence of plasmonic resonance and the synthesis of NPs by analyzing absorbance across 200–800 nm. Furthermore, the obtained absorbance spectrum could be employed to estimate the dimensions and morphology of the NPs. The analytical instrument utilized for this was a UV–vis spectrophotometer (UV-1800 Shimadzu UV Spectrophotometer) [19].

Particle size and zeta potential analysis

The size distribution and zeta potential of the synthesized NPs were measured by using the zeta sizer (Malvern Panalytical). The readings were measured in triplicate using automatic mode.

SEM (Scanning electron microscopy) and elemental analysis

The sample was prepared by sticking the carbon tape on the AI stub, wherein the sample was mounted over the carbon tape and the loose particles were removed using a blower. An examination of the prepared sample was conducted to assess the morphology, size, and shape of the synthesized NPs. Elemental analysis was carried out using the SEM–EDS instrument (Quanta 200) to verify the morphology, particle size, and purity of the prepared nanoparticles [19].

FTIR spectroscopy

The preparation of the sample involved uniform dispersion of NPs in a dry KBr medium, which was then packed into a disc. In the analysis, KBr serves as the standard using the FTIR instrument (Shimadzu IR Affinity-1 DRS 8000) [19].

In vitro investigation

Cytocompatibility evaluation

For evaluation of the cytocompatibility of the NPs, normal mouse fibroblast cells were cultured in Dulbecco's modified Eagle's medium supplemented with antibiotics and fetal bovine serum. A viable fibroblast cell suspension (50 µl), equivalent to 1×10^{-4} cells/ml, was seeded in a 96-well flat-bottom microplate and incubated at 37 °C with 95% humidity and 5% CO₂ overnight. Various concentrations (100%, 50%, 25%, 12.5%, 6.25% and 3.125%) of samples were introduced to allow the comprehensive assessment of cytotoxic effects of the NPs across wide spectrum, from high to very low concentrations. These ranges help to determine both the maximum tolerated dose as well as the lowest effective dose, ensuring a thorough evaluation of the NPs biocompatibility and potential therapeutic

index. Following an additional 48-h incubation, the wells were twice washed with PBS, and 20 µl of MTT staining solution was added to each well. The plate was then incubated at 37 °C. After 4 h, 100 µl of DMSO was introduced to dissolve the formazan crystals, and the absorbance was recorded at 570 nm using a microplate reader. The cell viability percentage was calculated using the provided Eq. (1) [20, 21].

$$\text{Cell viability (\%)} = \frac{\text{Mean absorbance of test sample}}{\text{Mean absorbance of negative control}} \times 100 \quad (1)$$

In vitro anticancer activity (MTT assay)

The MTT assay utilized HeLa (human cervical cell line) and MDA MB 231 (human breast cell line). Dulbecco's modified Eagle's medium with low glucose (Gibco, Invitrogen), fetal bovine serum (Gibco, Invitrogen), antibiotic antimycotic 100X solution (Thermo Fisher Scientific), and doxorubicin as the positive control were employed for the assay. Cells were seeded in a 96-well flat-bottom microplate and incubated at 37 °C with 95% humidity and 5% carbon dioxide overnight. Various concentrations (100%, 50%, 25%, 12.5%, 6.25% and 3.125%) of samples were introduced, followed by 48-h incubation. After washing the wells twice with PBS, 20 µl of MTT staining solution was added to each well, and the plate was incubated at 37 °C. After 4 h, 100 µl of DMSO was added to dissolve the formazan crystals, and absorbance was measured at 570 nm using a microplate reader. The relative anticancer potential was calculated wherein each experiment condition was performed in triplicate ($n=3$) to ensure the reliability and reproducibility of the results [20, 21].

In silico studies

Physicochemical properties and pharmacokinetic prediction of phytoconstituents

A literature review was conducted to identify phytoconstituents of *H. undatus*, resulting in the identification of 45 phytocompounds. Subsequently, these compounds underwent physicochemical parameters and pharmacokinetics prediction of the phytoconstituents which is a challenge in drug design and development. ADME (adsorption, distribution, metabolism, and excretion) parameters of the phytochemicals were calculated using Schrodinger's software through Maestro 12.4 interface (QikProp).

Network pharmacology

With an aim of understanding the drug's mechanism, the bioactive compounds screened for ADME were further analyzed via network pharmacology. Using the PubChem

database, we retrieved their canonical SMILES and searched the digep-pred database to predict their potential target genes. After removing duplicates using the UniProt database, the STRING database was employed to explore relevant biological pathways associated with these genes. Finally, a network was built in Cytoscape software using information on compound-protein and pathway-protein relationships, providing a visual map of how the drug's components might interact with cellular processes in cancer [22].

Molecular docking

The target protein EGFR for the docking studies was selected based on the network pharmacology in which the highly modulated proteins are responsible for greater anticancer activity. The protein structure was retrieved from RCSB Protein Data Bank (<https://www.rcsb.org/>) with PDB ID: IM17 (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib). Glide module of Schrodinger's software was utilized for docking to identify the binding interactions and orientation of ligands in the IM17 pocket. The 3D structures of ligands were prepared by using Schrodinger Maestro software and were used for docking. Then the protein was prepared by using a protein preparation wizard, which involves the assignment of the hydrogen bonds, bond orders, addition of hydrogens, optimization, minimization of the proteins, and deletion of waters beyond 5. Then the grid was generated and ligand was docked to the prepared protein the results were evaluated based on the docking score, glide energy, bond angle, bond length, and some other parameters.

Results

Phytochemical tests

The phytochemical tests were performed for various groups of phytochemicals among which carbohydrates, alkaloids, proteins, glycosides, flavonoids, polyphenols, organic acids, and tannins were present.

NPs synthesis

A biogenic synthetic protocol was employed which utilized *H. undatus* peel extract as a green alternative to create silver nanoparticles. The extract's biomolecules acted as both reducing agents, converting silver ions (Ag^+) into metallic silver (Ag^0), as well as stabilizing agents, preventing nanoparticle aggregation. The NPs were successfully synthesized and primarily indicated by the change in color (pinkish to brownish black). This is the chief indication of the formation of silver nanoparticles. Later the particles were centrifuged, dried, and further subjected to characterization [19].

Optimization

Varying conditions of temperature (4 °C, 280 °C, 60 °C, 80 °C), time of reaction (2 h, 4 h, 6 h, 24 h), pH (6, 8, 9, 12), concentration of AgNO_3 (1 mM, 2 mM, 4 mM, 6 mM), and concentration of extract (3 ml, 10 ml, 15 ml, 20 ml) were chosen to comprehensively evaluate the synthesis of silver nanoparticles under various conditions. Low temperatures and shorter reaction times help understand the initial nucleation, while higher temperatures and longer time evaluate stability. The pH range from mildly acidic to highly alkaline examines the influence of acidity on NPs formation, while varying AgNO_3 concentrations explore the effect of silver ion availability. Different extract volumes assess the role of reducing and stabilizing agents in NPs synthesis. Overall, these ranges aim to identify optimal conditions for efficient and reproducible nanoparticle production to optimize the particle size of the synthesized NPs. Optimal reaction conditions that displayed lower particle size were recorded at a wavelength of 448 nm with an absorbance of 0.836, using 1 mM silver nitrate, 10 ml extract, pH 8 for the extract, reaction time of 4 h, and a reaction temperature of 80 °C (Fig. 3) [19]. The observed UV-visible absorbance peak of the synthesized silver nanoparticles (AgNPs) at 448 nm is characteristic of surface plasmon resonance (SPR). This peak typically falls within the 410–455 nm range, as reported in the literature [16–18]. Given the strong dependence of SPR on nanoparticle size, shape, and dielectric properties, the observed peak at 448 nm suggests the formation of spherical AgNPs.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of silver nanoparticles biosynthesized using dragon fruit peel extract displayed distinctive peaks at various frequencies. The peak at 1590 cm^{-1} signifies the $\text{C}=\text{C}$ stretch, while 1623 cm^{-1} corresponds to the $\text{C}=\text{O}$ stretching. The peak at 2067 cm^{-1} is associated with $\text{C}\equiv\text{C}$, and 2850 cm^{-1} denotes aromatic $\text{C}-\text{H}$ of CHO. Additionally, a broad and strong band at 3464 cm^{-1} is indicative of $\text{O}-\text{H}$ stretching band of alcohols or phenols (Fig. 4) [19]. These functional groups interact with the nanoparticle surface through mechanisms such as π -electron interactions, oxygen coordination, and hydrogen bonding, forming a protective layer around the nanoparticles. This capping process is crucial for preventing nanoparticle aggregation, enhancing their stability in solution, and influencing their overall properties.

Particle size determination of synthesized NPs

The synthesized nanoparticles demonstrated an average particle size of 71.66 nm and a polydispersity index of 0.3754, and the zeta potential for the optimized batch

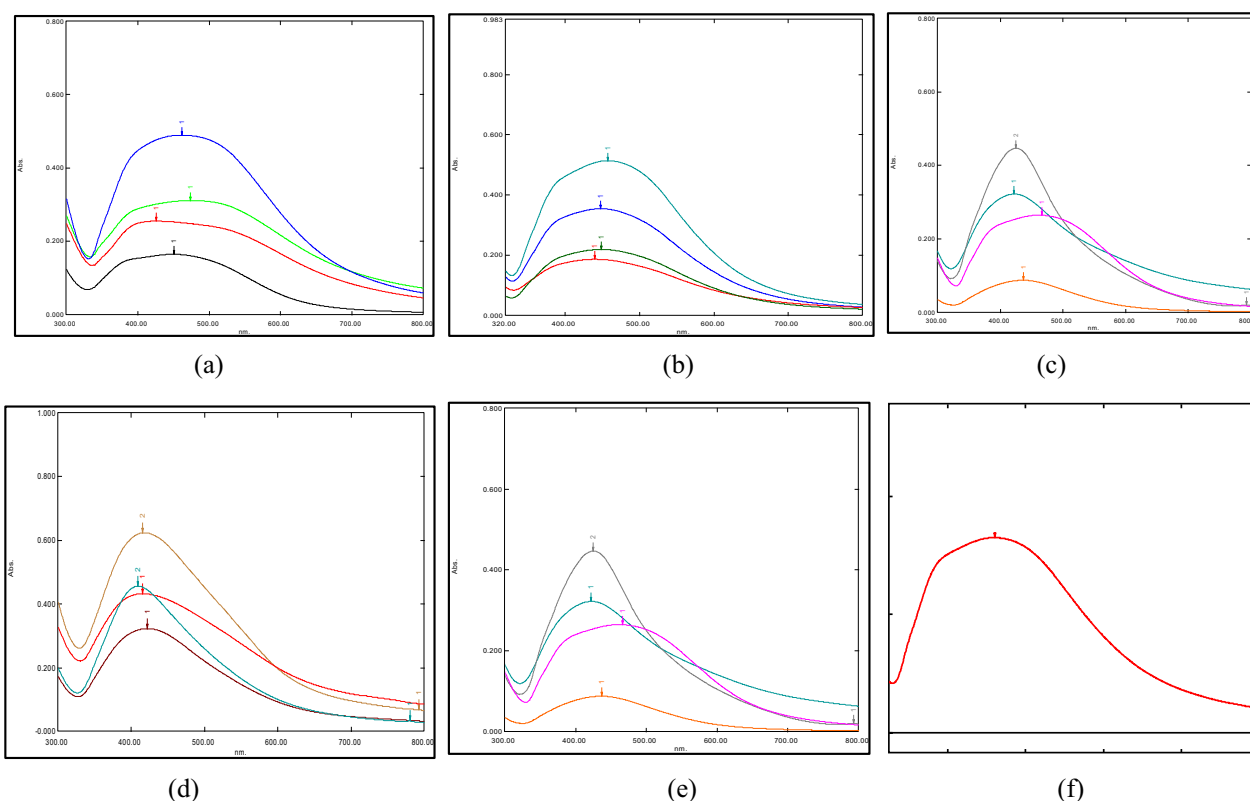


Fig. 3 UV-Vis spectra of synthesized NPs. **a** Effect of temperature of the reaction. **b** Effect of incubation time of the extract. **c** Effect of pH of the reaction. **d** Effect of concentration of AgNO_3 . **e** Effect of concentration of extract. **f** Spectrum of optimized synthesized NPs

is determined to be -38.52 mV. This finding suggests the favorable stability of the nanoparticles (Fig. 5). Conducting SEM analysis on the synthesized silver nanoparticles unveiled their particle morphology, indicating a spherical shape (Fig. 6) [19].

Energy-dispersive X-ray (EDAX) spectroscopy

It is a valuable spectroscopic technique for assessing the purity of synthesized nanoparticles. The analysis indicated that 79.5% of the surface composition of the nanoparticles is comprised of silver (Fig. 7) [19].

Cytotoxicity evaluation

The assessment of Vero cell growth, treated with NPs within the concentration range of 3.125 – 100 $\mu\text{g/ml}$, was compared to untreated healthy Vero cells, and the IC_{50} value was determined to be 126.99 $\mu\text{g/ml}$ ($\text{IC}_{50} > 100$ $\mu\text{g/ml}$), indicating non-toxicity within the tested concentration range. Morphological analysis (Fig. 8) comparing control cells (Fig. 8a) with NPs treated cells (Fig. 8b) at 100 $\mu\text{g/ml}$ revealed no significant alterations. The treated cells retained their typical shape and structure, with well-defined cellular boundaries similar to the control group. The lack of morphological changes is significant as it

indicates that the nanoparticles do not induce cytotoxic effects or stress responses. Maintaining normal morphology suggests that the cellular integrity and functions remain uncompromised, reinforcing the conclusion that the synthesized NPs are biocompatible and safe for Vero cells within the tested concentration range. Figure 9 illustrates the % viability of Vero cells incubated with NPs at various concentrations, suggesting that NPs do not hinder cell growth at any concentration (up to 100 $\mu\text{g/ml}$) and exhibit over 90–95% cell viability. In conclusion, the synthesized NPs are deemed safe based on the observed results [20, 21].

In vitro anticancer activity (MTT assay)

The evaluation of two distinct cancer cell lines, HeLa and MDA MB 231, treated with nanoparticles (NPs) across a concentration range of 3.125 – 100 $\mu\text{g/ml}$, was compared to the standard drug doxorubicin. The IC_{50} values for HeLa and MDA MB 231 cell lines were identified as 23.51 $\mu\text{g/ml}$ and 23.66 $\mu\text{g/ml}$, respectively. These values are critical in assessing the anticancer efficacy of the NPs. An IC_{50} value represents the concentration of a substance required to inhibit 50% of the cell population. The relatively low IC_{50} values for both HeLa and MDA MB 231

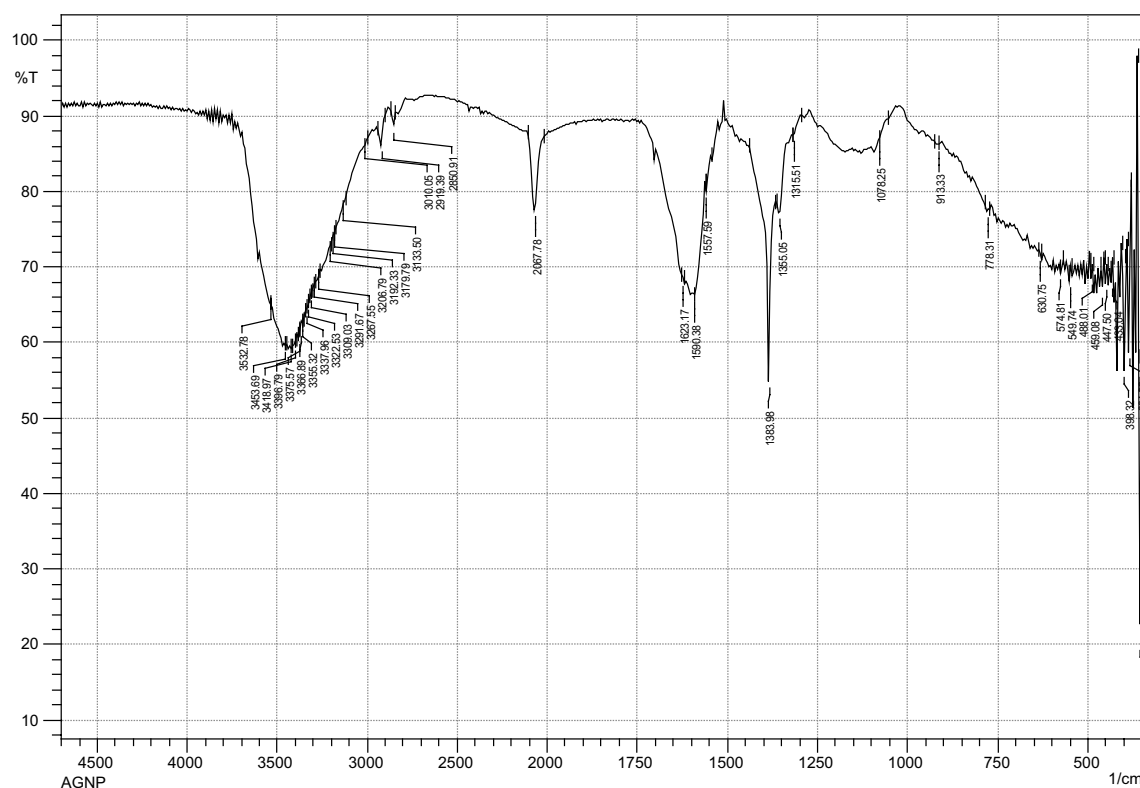


Fig. 4 IR Spectra of Synthesized NPs

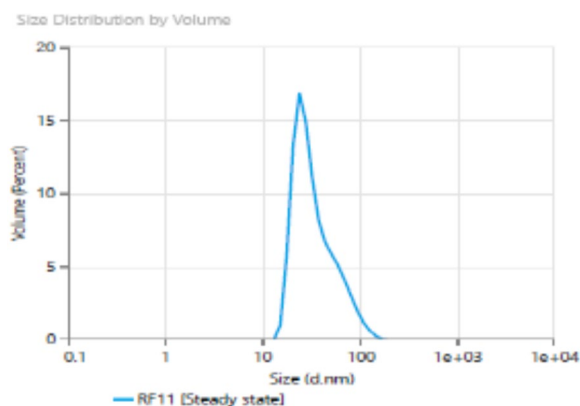


Fig. 5 Particle size analysis of synthesized NPs

cell lines indicate that the NPs are effective in inhibiting the proliferation of these cancer cells, when compared to the standard drug doxorubicin, which has IC₅₀ values of 2.15 µg/ml and 1.96 µg/ml against HeLa and MDA MB 231, respectively. These findings affirm that while the standard drug is more potent, the NPs still demonstrate significant anticancer activity. Results suggest that NPs can effectively hinder cancer cell growth and their IC₅₀ values indicate a promising potential for these NPs

as an alternative treatment to traditional chemotherapy. Morphological analysis in Fig. 10, contrasting the negative control (a, c) with NPs treated cells (b, d) at 100 µg/ml, demonstrated significant changes in cell morphology. Figure 11 (a, b) depicts the percentage of cell viability for HeLa and MDA MB 231 cancer cell lines when exposed to NPs at varying concentrations, indicating the hindrance of cancerous cell growth at all concentrations (up to 100 µg/ml). The MTT assay results highlight the capability of NPs to inhibit the proliferation of cancer cells [20, 21].

In silico studies

Physicochemical properties and pharmacokinetic prediction of phytoconstituents

Various parameters of selected bioactive compounds were examined to understand how their physicochemical properties affect their behavior in the human body. The physicochemical properties of phytoconstituents, such as molecular weight, lipophilicity (LogP), hydrogen bond donors and acceptors, along with polar surface area (PSA), solubility, and permeability, play a crucial role in predicting their oral bioavailability. Compounds with molecular weight under 500 daltons, LogP between 1 and 3, fewer than 5 hydrogen bond

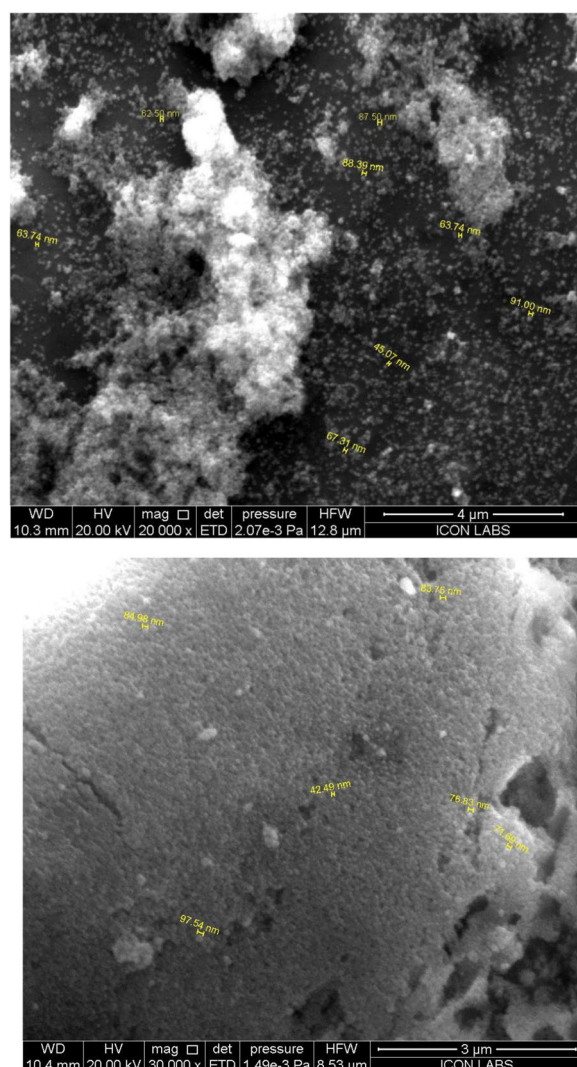


Fig. 6 SEM Analysis of Synthesized NPs

donors, and fewer than 10 hydrogen bond acceptors generally demonstrate better membrane permeability and absorption. PSA value below 140 Å² further supports this, as it facilitates effective membrane crossing. Adequate aqueous solubility ensures the compound can dissolve in gastrointestinal fluids, which is a prerequisite for absorption. Lastly, permeability determines the compound's ability to traverse biological membranes, a critical factor for absorption. By evaluating these properties, researchers can predict how well phytoconstituents will be absorbed when taken orally, guide the design of more bioavailable compounds, and streamline the drug development process, enhancing the likelihood of clinical success. The results are presented in Table 1. Among 45 phytoconstituents most of the

phytochemicals met the required parameter ranges, indicating their suitability. The compounds adhered to Lipinski's rule of five and showed drug-like scores above zero, indicating favorable oral bioavailability of the constituents derived from *H. undatus* [22].

Network pharmacology

The in silico network pharmacology and molecular docking studies were performed by screening the phytoconstituents for the drug-likeness, and its score was calculated based on Lipinski's rule of five. The selected phytoconstituents were subjected to network pharmacology. The network was constructed to determine the target proteins, pathways involved in the anticancer activity, and the phytoconstituents modulating these targets. The network pharmacology study identified kaempferol and quercetin as the most influential phytoconstituents with anticancer activity. Through the construction of a network, EGFR emerged as the most significant target protein, heavily involved in cancer-related pathways and transcriptional misregulation in cancer (Fig. 12). The study pinpointed several key genes associated with these pathways, including EGFR, CASP8, HMOX1, KRAS, ROCK1, MDM2, PRKACB, TRKACB, ITGAV, MMP2, CTNNB1, CCND2, NOTCH1, ARNT, IL15, IL23A, PRKCA, EGLN1, IL12B, among others listed in Table 2. Gene set enrichment analysis performed on quantitative expression data played a crucial role in elucidating the underlying mechanism of cancer by examining entire sets of genes associated with specific biological functions rather than focusing on individual genes. This method comprehensively analyzes how gene expression correlates with clinical phenotypes, such as cancer diagnosis. Table 3 presents a gene set enrichment analysis of various phytoconstituents from *Hylocereus undatus* targeting cancer-related protein molecules. It lists compounds along with their respective gene counts and the specific genes they target, highlighting potential therapeutic targets for cancer treatment. Thus, the results as seen in Tables 2 and 3 highlighted key pathways and gene sets involved in cancer, providing insights into the molecular processes driving the disease. Among the genes analyzed, EGFR emerged as a significant player, consistently appearing in the top gene sets associated with cancer-related pathways and transcriptional misregulation. This reinforced EGFR's critical role in cancer progression and underscored its potential as a therapeutic target. The comprehensive nature of gene set enrichment analysis helped clarify how EGFR and related genes contribute to cancer's complex biology, offering a deeper understanding of the disease's molecular basis and identifying potential avenues for targeted treatments [22].

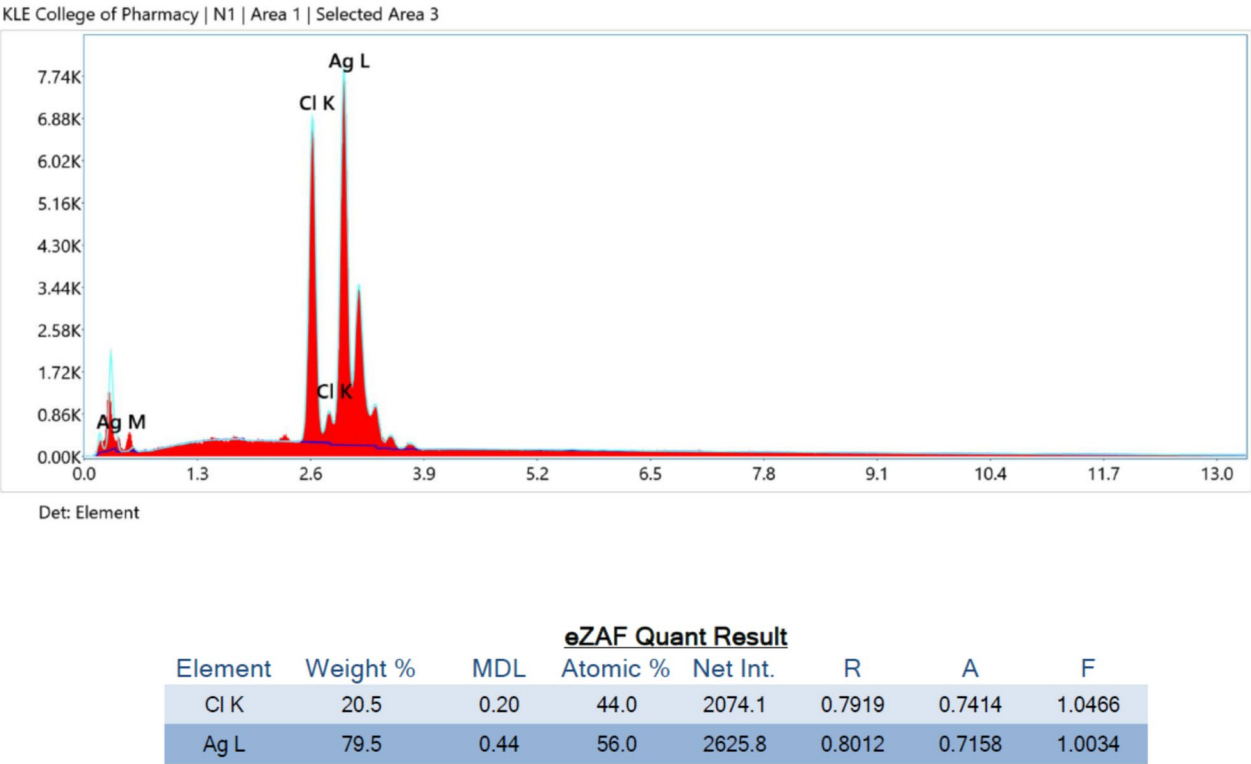


Fig. 7 Elemental analysis of synthesized AgNPs by EDAX

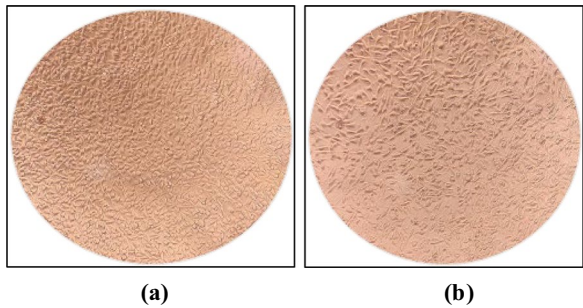


Fig. 8 Morphological analysis. **a** Shows untreated Vero cells. **b** Shows the presence of NPs at 100 µg/ml

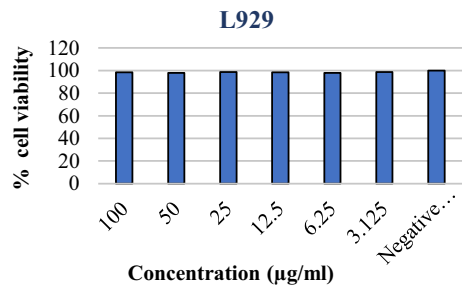


Fig. 9 Dose-dependent effect of NPs on the viability of Vero cells in vitro using MTT assay

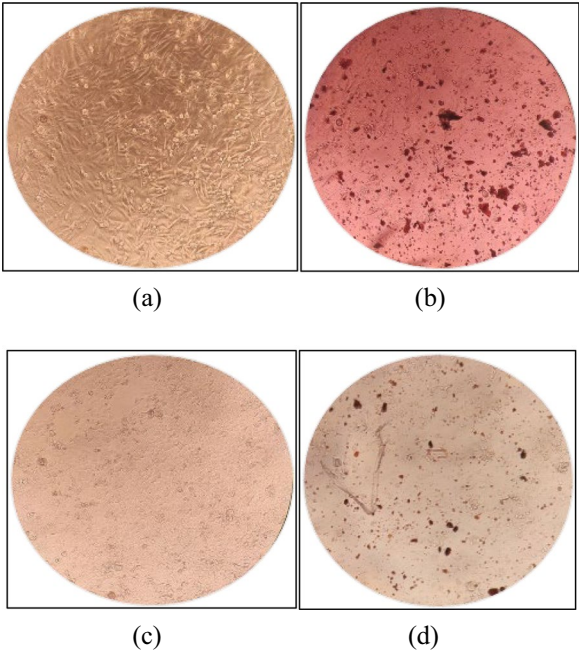


Fig. 10 Morphological analysis **a** Untreated MDA MB 231 cells, **b** NPs treated MDA MB 231 cells at 100 µg/ml, **c** Untreated HeLa cells and **d** NPs treated HeLa cells at 100 µg/ml

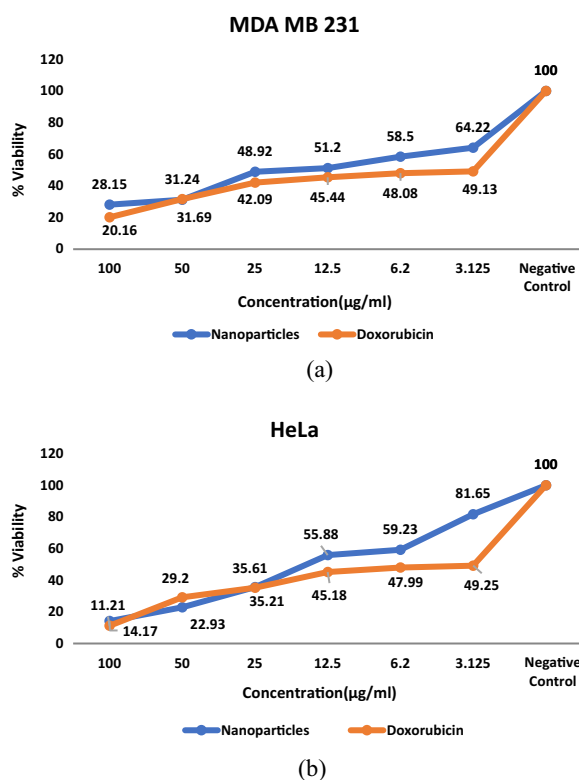


Fig. 11 Dose-dependent effect of NPs and std doxorubicin on the viability of **a** MDA MB 231 cells and **b** HeLa cells in vitro using MTT assay

Molecular docking

Epidermal growth factor receptor is a critical target in cancer therapy due to its role in regulating cell growth, survival, proliferation, and differentiation, often being overexpressed or mutated in various cancers. In this study, EGFR (PDB ID: 1M17) was selected for molecular docking analysis with phytoconstituents from dragon fruit. Table 4 depicts the docking energies and binding interactions between IM17 protein molecule and various phytocompounds like n-hexadecanoic acid, oleic acid, 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, campesterol, stigmasterol, γ -sitosterol, ergot-4,6,8(14),22-tetraen-3-one, β -carotene, rutin, kaempferol and quercetin. The standard used was erlotinib. All analyzed compounds showed binding with IM17 displaying docking scores ranging from -2.706 to -9.872 kcal/mol. The docking results revealed that quercetin and kaempferol, which were found to be the top modulating phytocompounds according to network pharmacology analysis, had significant binding affinities to EGFR, with docking scores of -9.87 and -8.625 kcal/mol, respectively, which were comparable with the standard EGFR inhibitor, erlotinib, displaying a docking score of -8.834 kcal/mol. This suggests that quercetin and kaempferol could effectively

inhibit EGFR activity, similar to erlotinib. The high binding affinity of these phytoconstituents to EGFR highlights their potential as alternative or complementary therapeutic agents in targeting EGFR-related signaling pathways in cancer, warranting future investigation into their efficacy and mechanism of action (Fig. 13).

Discussion

Our research investigated the potential of dragon fruit peel extract, a readily available and eco-friendly source, for developing anticancer therapies. This approach aligns well with the growing interest in sustainable drug discovery by utilizing abundant biological by-products. We successfully synthesized nanoparticles from the extract and employed various characterization techniques like UV-visible spectroscopy, particle size analysis, zeta potential and EDAX to confirm their presence, size, morphology, and elemental composition. The in vitro evaluation of these nanoparticles demonstrated promising results. They exhibited significant anticancer activity against human cancer cell lines representing both cervical (HeLa) and breast (MDA MB-231) cancers. Importantly, the nanoparticles displayed low cytotoxicity toward healthy mouse fibroblast cells, suggesting a potentially safe therapeutic profile.

The synthesis of nanoparticles using green chemistry principles ensures minimal environmental impact and promotes sustainability. Dragon fruit peel, often discarded as waste, provides a cost-effective and abundant raw material. The UV-visible spectroscopy confirmed the formation of nanoparticles through characteristic surface plasmon resonance peaks. Particle size analysis revealed nanoparticles within the optimal size range for cellular uptake, essential for effective drug delivery. The zeta potential measurements indicated the stability of the nanoparticles in suspension, while EDAX analysis confirmed the elemental composition, ensuring the integrity of the synthesized nanoparticles.

To gain deeper insights into the potential mechanism of action underlying these anticancer effects, we employed in silico techniques. An initial screening based on ADME and Lipinski's Rule of Five was conducted to identify drug-like candidates within the dragon fruit peel extract before further analysis. This screening ensured that the compounds present in the extract possessed favorable pharmacokinetic properties, essential for their efficacy as therapeutic agents. Network pharmacology, a computational approach that analyzes the complex interplay between drugs, their target proteins, and biological pathways, was then utilized. This analysis revealed kaempferol and quercetin, natural compounds present in the extract, as the most influential components responsible for the observed anticancer activity. Network analysis

Table 1 Physicochemical properties and pharmacokinetic prediction of phytoconstituents

Title	MolMW	Dipole	Volume	HBD	HBA	CNS	QPlogS	QPlogHERG	QPPCaco	QPlogBB	QPPMDCK	QPlogKhsa	%HOA	PSA	Rule of 5
n-Hexadecanoic acid	256.4	3.3	1113.7	1	2	-2	-5.4	-3.2	241.1	-1.4	135.2	0.51	87	50.5	1
(Z,Z)-9,12-Octadecadienoic acid	883.4	5.6	3338.1	0	6	-2	-16.9	-7.5	1201.7	-3.9	603.4	4.62	100	100.0	2
Oleic acid	282.5	3.3	1226.4	1	2	-2	-6.4	-3.7	240.5	-1.6	134.9	0.78	91	50.6	1
Trichloroacetic acid	163.4	4.5	406.9	1	2	0	-1.6	-0.6	304.2	0.3	1771.3	-0.77	79	48.1	0
Hexadecyl ester	424.7	3.3	1857.2	0	2	-2	-11.3	-6.6	3094.7	-1.7	1677.4	2.41	100	36.0	1
6-Tetradecanesulfonic acid, butyl ester	334.6	3.5	1338.1	0	4	-2	-6.2	-5.5	2931.4	-1.1	1583.5	0.75	100	44.0	1
1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester	278.3	0.7	999.6	1	4	-1	-4.1	-3.2	220.9	-1.0	123.0	0.06	91	74.9	0
Eicosane	404.5	4.0	1255.6	0	6	1	-5.2	-3.6	3791.5	0.1	2089.2	0.71	100	58.9	0
Heptacosane	380.7	0.0	1761.7	0	0	2	-17.0	-6.5	9906.0	2.2	5899.3	2.71	100	0.0	1
Campesterol	400.7	1.4	1420.1	1	2	0	-8.3	-4.6	4138.1	-0.2	2296.3	1.95	100	21.2	1
Stigmasterol	412.7	1.5	1447.2	1	2	0	-8.3	-4.4	4133.5	-0.2	2293.6	2.02	100	21.2	1
Squalene	410.7	0.2	1576.7	0	0	2	-14.2	-4.3	9906.0	1.7	5899.3	2.56	100	0.0	1
Octadecanol	268.5	3.4	1221.5	0	2	-2	-6.2	-5.3	1944.5	-1.2	1015.1	0.95	100	38.2	1
Nonacosane	408.8	0.0	1872.7	0	0	2	-18.1	-6.7	9906.0	2.3	5899.3	2.95	100	0.0	1
Octadecane	254.5	0.0	1211.8	0	0	2	-11.3	-5.3	9906.0	1.6	5899.3	1.50	100	0.0	1
γ-Sitosterol	414.7	1.4	1459.1	1	2	0	-8.3	-4.5	4139.7	-0.3	2297.3	2.02	100	21.2	1
Hexadecyl oxirane	268.5	3.0	1188.9	0	2	2	-8.5	-5.1	9906.0	0.7	5899.3	0.90	100	13.2	1
β-Amyrin	426.7	1.9	1362.3	1	2	1	-7.8	-3.5	4802.2	0.2	2697.1	2.00	100	19.0	1
Ergosta-4,6,8(14),22-tetraen-3-one	392.6	6.5	1368.9	0	2	0	-8.1	-4.7	2872.2	-0.2	1547.5	1.89	100	29.8	1
3,4,5-trihydroxybenzoic acid	952.7	6.0	2194.8	16	24	-2	-3.9	-4.8	0.0	-11.0	0.0	-1.60	0	496.5	3
β-carotene	536.9	0.9	2086.7	0	0	2	-19.5	-7.0	9906.0	2.2	5899.3	3.87	100	0.0	2
Rhodoxanthin	562.8	10.4	2079.5	0	4	-2	-12.3	-7.2	911.0	-2.1	447.3	2.78	100	57.8	2
1-propanol, 2-methyl (isobutanol)	74.1	1.9	393.5	1	2	1	0.0	-2.3	3314.0	0.1	1806.3	-0.69	94	22.3	0
Ribitol	152.1	3.3	535.0	5	8.5	-2	-0.3	-2.9	86.1	-1.7	34.9	-1.03	50	107.0	0
2-methyl malonic acid	118.1	5.8	418.5	0	2	-1	-0.3	1.2	9.9	-1.0	5.4	-1.11	49	95.3	0
1,3-Propanediol	76.1	3.9	363.7	2	3.4	-1	0.6	-2.4	839.3	-0.5	409.4	-0.98	73	46.3	0
Pentanoic acid, 4-methyl	116.2	2.8	512.4	1	2	-1	-0.7	-1.0	241.9	-0.5	135.7	-0.65	78	50.4	0
2,5-Methylene-di-l-thamnitol	178.2	2.0	590.6	3	8.5	-1	-0.9	-2.6	628.2	-0.6	299.3	-0.92	71	79.9	0
Benzene, 1-ethyl-4-methyl (4-Ethyltoluene)	120.2	0.1	558.4	0	0	2	-3.2	-3.7	9906.0	0.6	5899.3	0.20	100	0.0	0
Benzene, 1,3,5-trimethyl	120.2	0.0	560.0	0	0	2	-3.4	-3.5	9906.0	0.7	5899.3	0.24	100	0.0	0
Acetic acid, Octyl ester	172.3	3.1	797.5	0	2	0	-3.6	-4.4	2258.8	-0.5	1193.6	0.10	100	38.8	0
9-octadecenoic acid (2) (Oleic acid)	282.5	3.3	1226.4	1	2	-2	-6.4	-3.7	240.5	-1.6	134.9	0.78	91	50.6	1
1-Propyl 9,12,15-octadecatrienoate	320.5	2.8	1390.3	0	2	-1	-8.3	-6.0	3848.9	-0.8	2123.4	1.53	100	33.4	1
Retinal	284.4	5.1	1130.4	0	2	-1	-5.9	-4.7	1709.2	-0.8	883.0	0.98	100	37.6	1

Table 1 (continued)

Title	Mol MW	Dipole	Volume	HBD	HBA	CNS	QPlogS	QPlog HERG	QPPCaco	QPlogBB	QPPMDCK	QPlogKhsa	%HOA	PSA	Rule of 5
9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester	356.5	3.2	1454.9	2	5.4	-2	-6.2	-5.9	442.9	-2.4	205.1	0.57	100	77.5	0
3,4-Dihydroxybenzoic acid	154.1	3.6	505.7	3	3.5	-2	-0.8	-1.5	27.6	-1.2	13.0	-0.90	53	93.5	0
Chlorogenic acid	354.3	4.8	1043.2	6	9.65	-2	-2.5	-3.4	2.1	-3.3	0.8	-0.94	18	182.9	1
Caffeic acid	180.2	4.4	609.8	3	3.5	-2	-1.3	-2.2	22.4	-1.5	10.4	-0.80	54	95.6	0
Rutin	610.5	8.6	1570.3	9	20.55	-2	-2.3	-5.5	2.4	-4.2	0.7	-1.30	0	270.8	3
Kaempferol	286.2	4.5	845.0	3	4.5	-2	-3.1	-5.2	53.8	-1.9	21.0	-0.19	64	121.2	0
Coumaric acid	164.2	2.4	588.6	2	2.75	-2	-1.7	-2.3	62.2	-1.1	31.3	-0.66	67	74.1	0
Vanillin	152.1	3.7	549.3	1	3.5	-1	-1.1	-3.4	552.4	-0.7	260.5	-0.61	82	67.1	0
Ferulic acid	194.2	4.1	666.6	2	3.5	-2	-1.9	-2.3	61.9	-1.2	31.1	-0.61	67	81.5	0
Quercetin	302.2	5.4	866.2	4	5.25	-2	-2.9	-5.1	19.3	-2.4	6.9	-0.34	52	142.7	0
4- hydroxy- 3,5- dimethoxybenzoic acid	198.2	4.1	638.8	2	4.25	-1	-1.6	-1.6	82.8	-1.0	42.6	-0.71	67	86.5	0

*ADME parameters and their accepted range values: MW, molecular weight (≤ 500); HBD, hydrogen bond donor (≤ 5); HBA, hydrogen bond acceptor (≤ 10); QPlogS, aqueous solubility (-6.5 to 0.5); QPlogHERG, IC_{50} value for blocking HERG (human ether go related gene) potassium (K^+) channels; QPPCaco, permeability of Caco-2 cells (25 very poor to > 500 very great); QPlogBB, blood/brain partition coefficient (-3.0 to 1.2); QPPMDCK, Permeability of Madin-Darby canine kidney (MDCK) cells (25 very poor, > 500 very great); QPlogKhsa, predicting binding of drugs to human serum albumin (-1.5 to 1.5); HOA, human oral absorption ($> 80\%$; High, 25% ; Low)

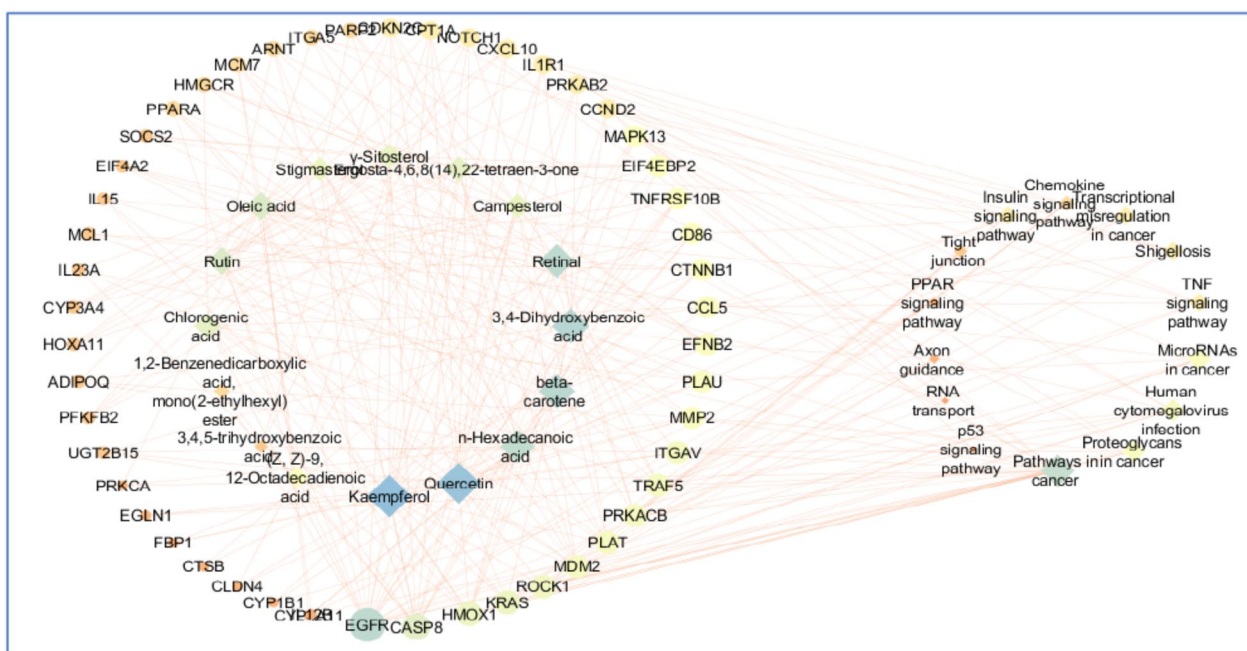


Fig. 12 Pathway and network analysis of *H. undatus* peel phytoconstituents

identified pathways associated with cancer and transcriptional misregulation in cancer as highly modulated pathways, potentially indicating that the nanoparticles might influence these pathways through their interaction with EGFR and other targets. Network pharmacology and gene set enrichment analysis identified EGFR as a major target for the analyzed compounds.

Furthermore, molecular docking simulations were performed to investigate the interaction between these key phytoconstituents and the protein EGFR, which is a well-established target in cancer therapy as it is frequently overexpressed in many cancers, playing a critical role in cell proliferation and survival. The docking simulations demonstrated a strong binding affinity between kaempferol and quercetin with EGFR, even surpassing the binding affinity observed with Erlotinib, a standard anticancer drug targeting EGFR. This suggests that these natural compounds might target and potentially inhibit EGFR activity, contributing to the nanoparticles' anticancer properties. Kaempferol and quercetin were thus identified as highly modulated components in the dragon fruit peel extract. These flavonoids are known for their anti-inflammatory, antioxidant, and anticancer properties. Their role in cancer pathways is multifaceted as they have shown to inhibit cancer cell proliferation by inducing cell cycle arrest. They modulate key signaling pathways involved in cell growth, such as the PI3K/Akt and MAPK pathways. These compounds promote apoptosis in cancer cells by activating pro-apoptotic proteins (e.g., Bax)

and inhibiting anti-apoptotic proteins (e.g., Bcl-2). This leads to the activation of caspases, the enzymes responsible for executing apoptosis. Kaempferol and quercetin inhibit angiogenesis, the process of new blood vessel formation that tumors require for growth and metastasis. They downregulate the expression of vascular endothelial growth factor (VEGF) and its receptor, thereby reducing blood supply to the tumor [23–30].

It was also evident from the results that MET 769, an amino acid residue within the IM17 EGFR protein, is a critical target for ligand binding. Compounds under study including ergot-4,6,8(14),22-tetraen-3-one, rutin, kaempferol, and quercetin displayed hydrogen bonding with the MET 769 residue, comparable to the standard drug erlotinib, which also exhibited hydrogen bonding with MET 769. The significance of MET 769 in the context of EGFR binding cannot be overstated. This residue, located within the kinase domain of EGFR, plays a crucial role in the stabilization of ligand interactions. By stabilizing the kinase domain, MET 769 influences the receptor's activation and subsequent signal transduction pathways that promote cell proliferation and survival [31–34]. In the context of our study, the ability of kaempferol and quercetin to interact strongly with MET 769 highlights their potential as effective EGFR inhibitors. This interaction not only underscores the therapeutic potential of these natural compounds but also provides a rationale for their use in the design of new drugs targeting EGFR. The strong interaction between ligands and MET

Table 2 Pathways and related genes involved in the network pharmacology of *Hylocereus undatus* and cancer

Sr. No	Pathway description	Gene count	Genes set involved in the pathway
1	Pathways in cancer	19	EGFR, CASP8, HMOX1, KRAS, ROCK1, MDM2, PRKACB, TRKACB, ITGAV, MMP2, CTNNB1, CCND2, NOTCH1, ARNT, IL15, IL23A, PRKCA, EGLN1, IL12B
2	Transcription misregulation in cancer	5	EGFR, PLAT, PLAU, CD86, CCND2
3	Proteoglycans in cancer	8	EGFR, KRAS, ROCK1, PRKACB, ITGAV, MMP2, MAPK13, ITGA5
4	MicroRNAs in cancer	7	EGFR, HMOX1, ROCK1, PLAU, CCND2, MCL1, CYP1B1
5	Shigellosis	6	ROCK1, TRAF5, CCL5, MAPK13, IL1R1, ITGA5
6	Chemokine signaling pathway	5	KRAS, ROCK1, PRKACB, CCL5, CXCL10
7	Axon guidance	3	KRAS, ROCK1, EFNB2
8	Tight junction	4	ROCK1, PRKACB, PRKAB2, CLDN4
9	TNF signaling pathway	6	EGFR, TRAF5, CCL5, MAPK13, CXCL10, IL15
10	Apoptosis	5	KRAS, TNFRSF10B, PARP2, MCL1, CTSB
11	Small cell lung cancer	2	ITGAV, TRAF5
12	p53 signaling pathway	2	EGFR, CCND2
13	PPAR signaling pathway	3	EGFR, CPT1A, CYP4A11
14	Prostate cancer	2	PLAU, PLAT
15	Cell cycle	1	EGFR
16	AMPK signaling pathway	1	EGFR

Table 3 Gene set enrichment analysis of protein molecules involved in the pathogenesis of cancer targeted by *Hylocereus undatus* phytoconstituents

Sr. No	Compound name	Gene count	Targets
1	<i>n</i> -Hexadecanoic acid	17	EGFR, CASP8, HMOX1, MMP2, CCL5, CD86, TNFRSF10B, CPT1A, ITGA5, MCM7, PPARA, IL23A, ADIPOQ, UGT2B15, PRKCA, IL12B, CYP4A1
2	(Z,Z)-9,12-Octadecadienoic acid	6	EGFR, CASP8, CPT1A, MCM7, PPARA, IL23A
3	Oleic acid	15	EGFR, CASP8, MDM2, MMP2, CCL5, CD86, CPT1A, ITGA5, MCM7, PPARA, IL23A, ADIPOQ, PRKCA, IL12B, CYP4A11
4	1,2-Benzene dicarboxylic acid, mono(2-ethylhexyl) ester	5	EGFR, CASP8, MDM2, CD86, ADIPOQ
5	Campesterol	12	EGFR, CASP8, MDM2, PLAT, EFNB2, EIF4EBP2, PARP2, HMGCR, SOCS2, CYP3A4, HOXA11, PFKFB2
6	Stigmasterol	10	EGFR, CASP8, MDM2, PLAT, EFNB2, EIF4EBP2, PARP2, HMGCR, HOXA11, PFKFB2
7	γ -sitosterol	12	EGFR, CASP8, MDM2, PLAT, EFNB2, EIF4EBP2, PARP2, HMGCR, SOCS2, CYP3A4, HOXA11, PFKFB2
8	Ergot-4,6,8(14),22-tetraen-3-one	11	EGFR, CASP8, MDM2, EFNB2, EIF4EBP2, PARP2, HMGCR, CYP3A4, HOXA11, PFKFB2, CLDN4
9	3,4,5-trihydroxy benzoic acid	4	HMOX1, CDKN2C, ITGAV, NOTCH1
10	β -carotene	11	EGFR, CASP8, HMOX1, PRKACB, TRAF5, CTNNB1, CD86, CCND2, MCM7, MCL1, EIF4A2
11	Retinal	10	EGFR, HMOX1, PRKACB, TRAF5, CTNNB1, CD86, MCM7, PPARA, EIF4A2, MCL1
12	3,4-dihydroxybenzoic acid	22	EGFR, HMOX1, KRAS, PLAT, PRKACB, TRAF5, ITGAV, MMP2, PLAU, EFNB2, CCL5, CTNNB1, CD86, TNFRSF10B, MAPK13, PRKAB2, IL1R1, NOTCH1, ITGA5, SOCS2, ADIPOQ, UGT2B15
13	Chlorogenic acid	9	EGFR, CASP8, HMOX1, PLAT, PLAU, TNFRSF10B, CXCL10, MDM2, HMGCR
14	Rutin	14	EGFR, HMOX1, KRAS, PLAT, ITGAV, PLAU, CTNNB1, TNFRSF10B, PRKAB2, IL1R1, CXCL10, NOTCH1, CDKN2C, ARNT
15	Kaempferol	27	EGFR, CASP8, HMOX1, KRAS, ROCK1, MDM2, PLAT, ITGAV, MMP2, PLAU, EFNB2, CTNNB1, TNFRSF10B, MAPK13, PRKAB2, IL1R1, CXCL10, NOTCH1, CPT1A, CDKN2C, ARNT, IL15, UGT2B15, EGLN1, FBP1, CLDN4, CYP1B1
16	Quercetin	21	EGFR, CASP8, HMOX1, KRAS, ROCK1, MDM2, ITGAV, MMP2, PLAU, EFNB2, CTNNB1, TNFRSF10B, MAPK13, PRKAB2, IL1R1, CXCL10, NOTCH1, CPT1A, CDKN2C, ARNT, IL15

Table 4 Ligand–protein interactions and docking scores of *H. undatus* phytoconstituents and IM17

Sr NO.	Phytochemicals from <i>H. undatus</i>	Docking score (XP)	Glide energy (kcal/mol)	Ligand–amino acid interactions	Amino acid residues	Bond length (Å)
1	<i>n</i> -Hexadecanoic acid	−3.02	−29.685	O of ligand to Lys 704	Lys 704	2.73
2	Oleic acid	−2.989	−30.023	O of ligand to Lys 704	Lys 704	1.87
3	1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl)ester	−4.537	−32.137	O of ligand to Lys 721	Lys 721	1.67
4	Campesterol	−3.928	−25.476	–	–	–
5	Stigmasterol	−2.765	−29.549	–	–	–
6	γ-sitosterol	−2.706	−27.723	OH of ligand to ASP 776	ASP 776	1.85
7	Ergot-4,6,8(14),22-tetraen-3-one	−5.043	−29.171	O of ligand to MET 769	MET 769	1.91
8	β-carotene	−4.314	−47.074	OH of ligand to GLU 780	GLU 780	1.74
				H of ligand to ASP 776	ASP 776	2.50
9	Rutin	−8.653	−67.762	OH of ligand to ARG 817	ARG 817	2.02
				OH of ligand to MET 769	MET 769	1.80
10	Kaempferol	−8.625	−39.722	OH of ligand to MET 769	MET 769	1.70
				O of ligand to MET 769	MET 769	1.82
11	Quercetin	−9.872	−44.4	OH of ligand to ASP 831	ASP 831	2.33
				OH of ligand to ARG 817	ARG 817	2.02
				OH of ligand to MET 769	MET 769	1.80
12	Erlotinib	−8.834	−56.108	O of ligand to CYS 773	CYS 773	2.32
				N of ligand to MET 769	MET 769	1.62

769 suggests that targeting this region can be a successful strategy for designing anticancer drugs. Drugs that mimic this interaction by forming hydrogen bonds with MET 769 can effectively compete with natural EGFR ligands, thereby inhibiting the receptor's signaling pathway and ultimately hindering cancer cell growth. Several existing EGFR inhibitors, like Erlotinib, have been shown to interact with MET 769 in docking studies, validating this approach for anticancer drug development. Thus, this knowledge will be instrumental in designing new and potent anticancer drugs that can effectively inhibit EGFR signaling and disrupt cancer cell proliferation.

Thus, the findings from our study have significant implications for the development of novel anticancer drugs targeting EGFR and other identified pathways. The use of dragon fruit peel extract and its key phytoconstituents, presents a promising approach for creating effective and sustainable cancer therapies. The green synthesis approach using dragon fruit peel extract aligns with the growing emphasis on environmentally friendly practices in drug development. Utilizing biological by-products not only reduces waste but also provides a cost-effective source for raw materials. This sustainable approach could revolutionize the production of nanoparticles, making it more accessible and affordable. The identification of EGFR as a key target provides a clear direction for drug development. By focusing on compounds that interact

with EGFR, particularly at the MET 769 residue, new drugs can be designed to effectively inhibit EGFR signaling pathways. This inhibition could prevent cancer cell proliferation and induce apoptosis, leading to more effective cancer treatments.

The strong binding affinities observed in the docking studies suggest that kaempferol and quercetin have the potential to be highly effective as anticancer agents. Their ability to bind more strongly than erlotinib indicates that these natural compounds might offer superior therapeutic benefits. This could lead to the development of more potent drugs with fewer side effects.

The insights gained from network pharmacology and molecular docking can contribute to the advancement of personalized medicine. By understanding the specific interactions between compounds and their targets, therapies can be tailored to individual patients based on their genetic and molecular profiles. This personalized approach could improve treatment outcomes and reduce adverse effects.

Overall, this research paves the way for further exploration of dragon fruit peel extract as a promising source for future anticancer drug development. By leveraging natural resources and advanced computational techniques, we can develop effective and sustainable cancer therapies. The integration of green chemistry principles, in vitro evaluations, and in silico analyses creates a

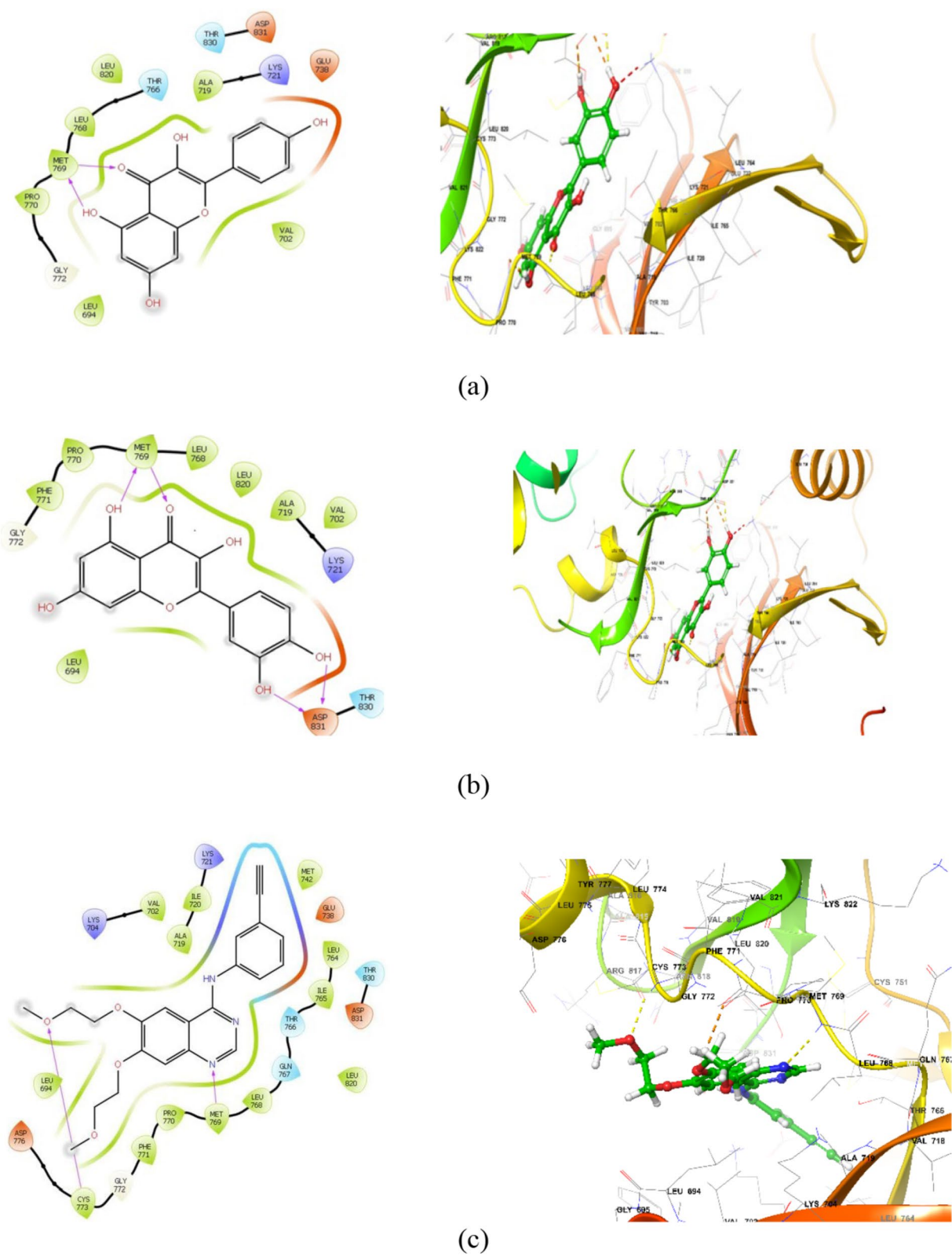


Fig. 13 Molecular docking with IM17. **a** 2D and 3D images of the docked kaempferol. **b** 2D and 3D images of docked quercetin. **c** 2D and 3D images of docked standard erlotinib

robust framework for the discovery and optimization of novel anticancer agents, ultimately contributing to the advancement of personalized and precision medicine in oncology.

Conclusion

In conclusion, our study unveils the remarkable potential of *Hylocereus undatus* fruit peel extract in the development of eco-friendly and effective anticancer therapies. The synthesis of nanoparticles from dragon fruits and their robust anticancer activity against HeLa and MDA MB-231 cells mark a significant advancement in sustainable drug discovery. This approach not only underscores the therapeutic potential of the compounds but also paves the way for environmentally conscious drug development, laying groundwork for future research and advancements.

The in silico studies complement the experimental findings by providing deeper insights into the anticancer potential of the synthesized nanoparticles. While the experimental results showed significant cytotoxicity against HeLa and MDA MB-231 cancer cell lines and minimal toxicity to healthy cells, the in silico analyses revealed that kaempferol and quercetin, key phytoconstituents, strongly bind to the MET 769 residue in the EGFR protein. This interaction is crucial as MET 769 stabilizes ligand binding and influences EGFR activation, which is critical for cancer cell proliferation. The strong binding affinities of these compounds, confirmed by molecular docking, align with the observed experimental effects, validating the nanoparticles' targeted anticancer properties. This integrated approach highlights the nanoparticles' potential as an eco-friendly and effective treatment option for cancer, ultimately aiming to improve patient outcomes and contribute to the fight against cancer.

Further investigations, including pre-clinical animal studies to validate anticancer efficacy and safety, and exploration of additional bioactive compounds from dragon fruit peel extract, are crucial. Such endeavors aim to develop targeted anticancer therapies, potentially enhancing treatment efficacy and reducing toxicity. By leveraging the unique binding properties of these phytoconstituents, future research can focus on creating potent anticancer agents that inhibit EGFR signaling with minimal side effects, offering a beacon of hope for more effective and sustainable cancer treatments.

Abbreviations

<i>H. undatus</i>	<i>Hylocereus undatus</i>
AgNPs	Silver nanoparticles
EGFR	Epidermal growth factor receptor
SEM	Scanning electron microscopy
EDAX	Energy-dispersive X-ray

FTIR	Fourier transform infrared spectroscopy
HeLa	Human cervical cell line
MDA MB 231	Human breast cell line
AgNO ₃	Silver nitrate
SPR	Surface plasmon resonance
MET 769	Methionine

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Author contributions

KR conducted practical work, data curation and writing of manuscript; PS contributed to design, validation and supervision of work, writing, reviewing and editing of manuscript.

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Data availability

Raw data were generated and will be provided from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors (KR and PS) declare that they have no competing interests.

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