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Research Article

Inhibition Potential and Molecular Mechanisms of Longan Flower Water Extract in Lung Adenocarcinoma Cells

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Abstract

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Lung adenocarcinoma is the most common subtype of non-small cell lung cancer, characterized by high incidence and poor survival. Natural plant-derived compounds offer potential sources for anticancer drug development. This study investigated the inhibition effects and molecular mechanisms of longan flower water extract (LFWE) in H1975 lung adenocarcinoma cells. LFWE significantly reduced H1975 cell viability and induced notable morphological changes. Mechanistically, LFWE activated autophagy, evidenced by increased LC3-II/LC3-I ratios and decreased P62 levels, and promoted lysosome-mediated degradation of mutant epidermal growth factor receptor (EGFR), leading to inhibition of downstream mTOR signaling. However, LFWE showed a degree of inhibition activity toward non-malignant lung cells, potentially imposing limitations. Further studies on its safety and translational application are necessary. In summary, this study provides preliminary evidence for exploring LFWE as a potential therapeutic strategy for lung adenocarcinoma.

Key words: Longan flower water extract, Lung adenocarcinoma, Autophagy, EGFR.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases (Leiter *et al*. 2023). Despite advances in targeted therapy and immunotherapy, the overall five-year survival rate remains low (Luo *et al*. 2022). Among NSCLC subtypes, lung adenocarcinoma is the most prevalent, frequently driven by oncogenic alterations such as mutations in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma virus (KRAS), or anaplastic lymphoma kinase (ALK) fusions (Devarakonda *et al*. 2015; Chapman *et al*. 2016). These genetic complexities underscore the ongoing need for alternative or complementary therapeutic approaches.

Natural products have long been recognized as valuable sources of bioactive compounds with anticancer potential (Markman & Mekhail 2002; Acquaviva *et al*. 2022). Longan (*Dimocarpus longan* Lour.), a widely cultivated fruit tree in subtropical Asia, is not only an important agricultural crop but also a traditional medicinal plant. Longan flowers are abundant byproducts of cultivation, which are rich in polyphenols, flavonoids, and tannins, with demonstrated

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antioxidant and anti-inflammatory properties (Ho *et al*. 2007; Hsieh *et al*. 2008). Bioactive constituents such as gallic acid, epicatechin, procyanidin A2, and corilagin have been identified (Hsieh *et al*. 2008; Sheu *et al*. 2016), several of which exhibit anticancer activity (Shay *et al*. 2015; Gupta *et al*. 2019). Previous studies reported inhibitory effects of longan flower extracts on colorectal, liver, cervical, and breast cancer cells (Lin *et al*. 2012).

However, the effects of longan flower extracts on lung adenocarcinoma, particularly at the mechanistic level, remain poorly understood. In this study, we systematically investigated the cytotoxicity and underlying molecular mechanisms of longan flower water extract (LFWE) in EGFR-mutant lung adenocarcinoma cells. Our findings aim to clarify whether LFWE may hold potential as adjunctive strategies for lung cancer treatment.

MATERIALS AND METHODS

Preparation of LFWE

Fresh longan flowers were purchased from local farmers (23.2755°N, 120.4908°E) in Dongshan District, Tainan, Taiwan. A voucher specimen (Batch No. TARI-L01) has been deposited at Taiwan Agricultural Research Institute for future reference. The flowers were sun-dried for approximately 3 d until moisture content was below 10%, as determined using a moisture analyzer (MX-50, A&D Company, Limited, Tokyo, Japan). The dried flowers were then extracted with 20 volumes of double-distilled water at 60℃ using ultrasonic-assisted extraction (ES-600N, Taiwan Supercritical Technology Co., Ltd, Changhua, Taiwan; frequency 40 kHz, power 600 W) for 1 h. The extract was filtered through Whatman™ No. 1 filter paper (Cytiva, Marlborough, MA, USA) to remove residues, concentrated under reduced pressure, and subsequently lyophilized into powder. The extraction yield was calculated, and the lyophilized powder was stored at -20℃ until use.

Cell culture

LFWE cytotoxicity was assessed in one lung cancer cell line and two non-malignant lung cell lines. The lung cancer cell line H1975, harboring the EGFR-L858R/T790M mutation, was purchased from Elabscience Biotechnology Co., Ltd. (Wuhan, China). Normal lung epithelial cells (BEAS-2B) were purchased from the JCRB Cell Bank (Osaka, Japan), and normal lung fibroblasts (WI-38) were purchased from the Bioresource Collection and Research Center, Food Industry Research and Development Institute (Hsinchu, Taiwan). H1975 cells were cultured in Roswell Park Memorial Institute 1640 medium (Gibco, Thermo Fisher Scientific Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS), while BEAS-2B and WI-38 cells were maintained in Minimum Essential Medium (Gibco, Thermo Fisher Scientific Inc., Waltham, MA, USA) containing 10% FBS. All cell lines were cultured at 37℃ in a humidified incubator with 5% CO_2 and passaged every 2–3 d.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay

The cytotoxic effects of LFWE on lung cancer and non-malignant lung cell lines were evaluated using the MTT assay. Cells were seeded in 96-well plates at a density of 5×10^4 cells per 100 μL per well and allowed to adhere for 24 h. They were then treated with various concentrations of LFWE (0–800 μg mL^{-1}) for 24–72 h. Cell viability was determined by adding MTT (Sigma-Aldrich Corporation, St. Louis, MO, USA) to each well and incubating at 37℃ for 4 h. The resulting formazan crystals were dissolved in dimethyl sulfoxide (DMSO; Sigma-Aldrich Corporation, St. Louis, MO, USA), and absorbance was measured at 570 nm.

Cell cycle analysis

To determine whether LFWE regulates the cell cycle of lung cancer cells, H1975 cells were seeded in 6 cm culture dishes at a density

of 5×10^4 cells $dish^{-1}$ and allowed to adhere for 24 h. Cells were then treated with various concentrations of LFWE (0–400 μg mL^{-1}) for 48 h. After treatment, cells were harvested by trypsinization, collected by centrifugation at 1,500× *g* for 10 min, and washed with phosphate-buffered saline (PBS). The cell pellets were fixed in 70% ethanol at -20℃ for 30 min, followed by centrifugation to remove ethanol. Fixed cells were resuspended in 50 μL PBS containing propidium iodide (100 μg mL^{-1}; Elabscience, Wuhan, China) and 10 μL RNase A (Thermo Fisher Scientific Inc., Waltham, MA, USA), and incubated at 37℃ for 30 min in the dark. Cell cycle distribution was analyzed using a flow cytometer (CytoFLEX, Beckman Coulter Inc., Brea, CA, USA) with 10,000 events collected per sample. Data were processed and analyzed with CytExpert software (Beckman Coulter, Brea, CA, USA).

Apoptosis analysis

To evaluate whether LFWE induces apoptosis, lung cancer cell line H1975 was seeded at a density of 2.5×10^5 cells per dish and treated with LFWE at different concentrations (100, 200, and 400 μg mL^{-1}) for 48 h. After treatment, cells were harvested by trypsinization, washed with 1.0 mL cold PBS, and centrifuged at 1,800 rpm for 15 min. The cell pellets were then resuspended and stained using the fluorescein isothiocyanate (FITC) Annexin V/PI (propidium iodide) apoptosis detection kit (Elabscience, Wuhan, China) according to the manufacturer's protocol, followed by incubation at 37℃ for 15 min in the dark. Apoptotic cell populations were analyzed using Beckman CytoFLEX flow cytometry with 10,000 events acquired per sample. Data were processed with CytExpert software.

Western blot analysis

H1975 lung cancer cells were seeded in 6-cm culture dishes at a density of 5×10^5 cells and allowed to adhere for 24 h. Cells were then treated with different concentrations of LFWE (100, 200, and 400 μg mL^{-1}) for the indicated time periods. Following treatment, cells were washed with PBS containing 1% Na_3VO_4 and lysed with 40 μL of lysis buffer. Lysates were vortexed to disrupt membranes and centrifuged at 13,000× *g* for 10 min at 4℃. The supernatant (cell lysate) was collected, and protein concentrations were determined by the Bradford assay using bovine serum albumin (BSA) as a standard.

Equal amounts of protein (30 μg) were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE, 10%) and transferred onto polyvinylidene difluoride (PVDF) membranes (PerkinElmer, Waltham, MA, USA). Membranes were blocked with 5% non-fat milk for 1 h at room temperature, then incubated overnight at 4℃ with the following primary antibodies: anti-EGFR (GTX121919, GeneTex, Inc., Irvine, CA, USA), anti-phospho-mTOR (Ser2448; GTX132803, GeneTex, Inc., Irvine, CA, USA), anti-phospho-AKT (Ser473; #4060, Cell Signaling Technology, Inc., Danvers, MA, USA), anti-LC3B (GTX127375, GeneTex, Inc., Irvine, CA, USA), anti-SQSTM1/p62 (GTX100685, GeneTex, Inc., Irvine, CA, USA), and anti-β-actin (GTX109639, GeneTex, Inc., Irvine, CA, USA). All primary antibodies were used at a dilution of 1:1,000, except β-actin (1:5,000). After washing, membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies for 1 h at room temperature, and protein bands were visualized using enhanced chemiluminescence detection.

Statistical analysis

All data are expressed as mean ± standard deviation (*SD*), with n indicating the number of independent experiments. Error bars represent *SD*. Statistical analyses were conducted using GraphPad Prism software (version 9.0.0; GraphPad Software, San Diego, CA, USA). Depending on the experimental design, comparisons among multiple treatment groups were performed using one-way analysis of variance (ANOVA) followed by either Dunnett's or Tukey's post hoc test, as appropriate. For comparisons between two groups, unpaired Student's *t*-tests were applied. A P value < 0.05 was considered statistically significant.

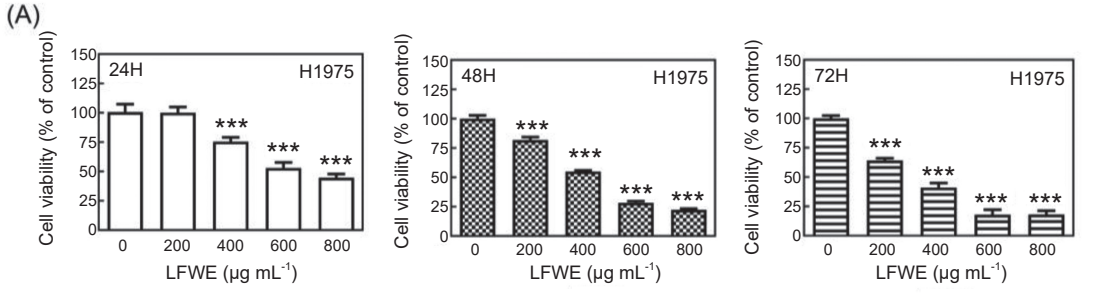
RESULTS AND DISCUSSION

LFWE inhibits H1975 cell growth and alters cellular morphology

To evaluate the cytotoxic effects of LFWE on lung cancer, we selected the human non-small cell lung carcinoma cell line H1975. This cell line harbors EGFR mutations (L858R and T790M), which are clinically associated with resistance to first- and second-generation tyrosine kinase inhibitors (TKIs), making it a relevant *in vitro* model for exploring potential alternative therapies.

MTT assays revealed that LFWE reduced H1975 cell viability in a dose- and time-dependent manner. The IC50 values decreased from 1,599.2 μg mL^{-1} at 24 h to 505.1 μg mL^{-1} at 48 h, and further to 190.0 μg mL^{-1} at 72 h (Fig. 1A and B), indicating cumulative suppression of cellular metabolic activity. Although high concentrations were required for substantial inhibition, the progressive reduction in IC_{50} suggests increased cellular sensitivity upon prolonged exposure.

Examination of cellular morphology showed marked changes following LFWE treatment. Cells shifted from an elongated, spindle-like appearance to a rounded and shrunken morphology, accompanied by a notable reduction in cell density (Fig. 1C). These alterations are consistent with cytotoxic effects. Collectively, these findings demonstrate that LFWE suppresses H1975 cell growth and affects cell morphology, prompting further investigation into potential underlying mechanisms such as cell-cycle perturbation, apoptosis, or other non-apoptotic cytotoxic processes.



(B)

H1975

IC_{50} of LFWE (μg mL^{-1})	
24 H	1599.2
48 H	505.1
72 H	190.0

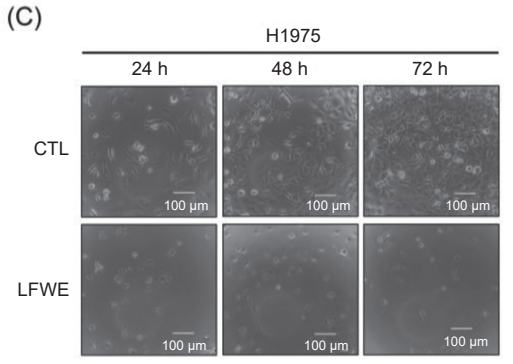


Fig. 1. Longan flower water extract (LFWE) inhibits viability of H1975 lung cancer cells. (A) H1975 cells were treated with LFWE (0–800 μg mL^{-1}) for 24, 48, and 72 h. The bar graph show the cell viability determined by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Data represent the mean ± *SD* (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test comparing each treatment group with the control (0 μg mL^{-1}). Significant differences are shown ($^{***}P < 0.001$). (B) IC_{50} of LFWE in H1975 cells. (C) Morphological changes of three lung cancer cell lines after treatment with LFWE (800 μg mL^{-1}) for 24–72 h. CTL: control.

LFWE exhibits differential cytotoxicity between cancerous and normal lung cells

To evaluate the cytotoxic effects of LFWE, we examined its impact on the human non-small cell lung carcinoma cell line H1975 as well as two non-malignant lung cell lines: bronchial epithelial BEAS-2B and fibroblast WI38. These non-malignant cell types represent distinct compartments of lung tissue and provide an initial assessment of potential toxicity toward normal cells. Cells were treated with LFWE at 0–800 μg mL^{-1} for 72 h, and viability was measured using the MTT assay.

LFWE reduced H1975 viability in a dose-dependent manner, with 200 μg mL^{-1} causing moderate inhibition (66.2% viability) and higher concentrations (400–800 μg mL^{-1}) inducing substantial suppression (44.8–20.5% viability) (Fig. 2A). Importantly, BEAS-2B cells were already markedly affected at 200 μg mL^{-1} (45.1% viability), and WI38 fibroblasts displayed partial inhibition (67.4% viability), indicating that LFWE exerts cytotoxic effects on non-malignant cells even at relatively low doses. At concentrations above 600 μg mL^{-1}, H1975 cells were suppressed slightly more than either BEAS-2B or WI38, reflecting modest preferential activity toward cancer cells. For example, at 800 μg mL^{-1}, the viability of WI38 and BEAS-2B cells were significantly higher than that of H1975 cells (Fig. 2B).

Overall, these results reveal a dose- and cell type–dependent cytotoxic profile. The early sensitivity of BEAS-2B epithelial cells at 200 μg mL^{-1} and the limited differential between malignant and non-malignant cells highlight a narrow therapeutic window. These findings underscore the necessity of carefully evaluating the molecular mechanisms underlying LFWE's effects on cancer versus normal lung cells to inform its potential translational application and safety profile.

LFWE perturbs cell-cycle progression and induces a modest apoptotic response in H1975 cells

Flow cytometric analysis revealed that LFWE altered H1975 cell-cycle distribution. The G1 fraction decreased progressively with increasing dose (from ~58% to ~48%), while the S-phase fraction increased (from ~5% to ~16%), and G2/M remained relatively stable. The sub-G1 population, typically associated with apoptotic DNA fragmentation, increased slightly (from < 1% to ~2%) (Fig. 3A). These results suggest that LFWE disrupts normal cell-cycle progression, promoting premature

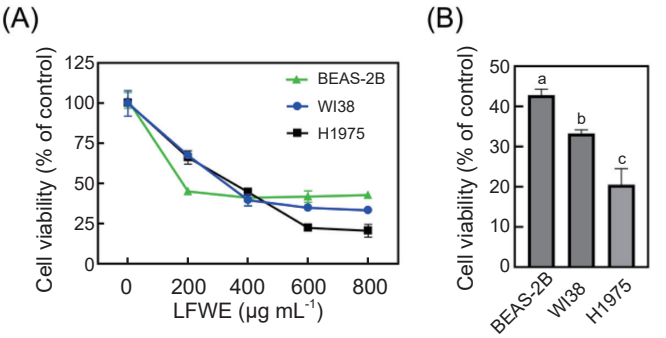


Fig. 2. Effects of longan flower water extract (LFWE) on the viability of lung cancer and normal lung cells. (A) H1975 lung adenocarcinoma cells and two normal lung cell lines (bronchial epithelial BEAS-2B and fibroblast WI38) were treated with LFWE (0–800 μg mL^{-1}) for 72 h. Cell viability was determined by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Data represent the mean ± *SD* (n = 3). (B) The bar graph compares cell viability at 800 μg mL^{-1} LFWE. Data represent the mean ± *SD* (n = 3). Statistical significance between cell types was determined by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test; groups not sharing the same letter are significantly different.

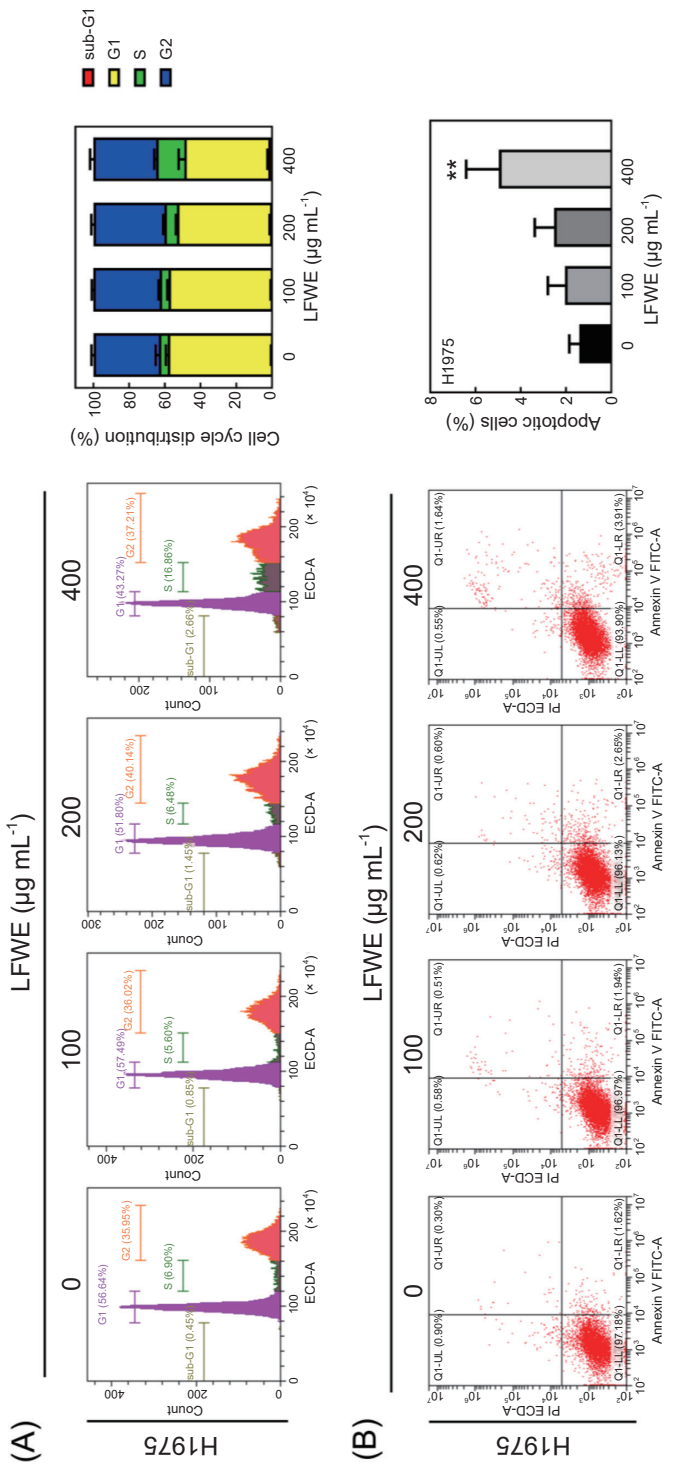


Fig. 3. Longan flower water extract (LFWE) enhances subG1 population and induces minor apoptotic responses in H1975 lung adenocarcinoma cells. (A) H1975 cells were treated with LFWE (0–400 μg mL^{-1}) for 48 h, stained with propidium iodide (PI), and analyzed for cell cycle distribution by flow cytometry. (B) H1975 cells were treated with LFWE (0–400 μg mL^{-1}) for 48 h, co-stained with Annexin V-FITC (fluorescein isothiocyanate) and PI, and analyzed for apoptosis by flow cytometry. Data represent the mean ± *SD* ($n = 3$). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test comparing each treatment group with the control (0 μg mL^{-1}). Significant differences are shown ($^{**}P < 0.01$).

or dysregulated entry into S phase, which may compromise genomic integrity and contribute to growth suppression.

Annexin V/propidium iodide staining confirmed that LFWE induced apoptosis in a dose-dependent manner, but the effect was modest, reaching approximately 6% at 400 μg mL^{-1} (Fig. 3B). This limited apoptotic response suggests that apoptosis alone cannot fully account for the observed decrease in viability, and additional non-apoptotic cytotoxic mechanisms are likely involved.

LFWE induces autophagy-related molecular changes in H1975 cells

Autophagy is closely associated with cancer cell growth regulation (Hsin *et al*. 2011; Jung *et al*. 2020). To explore potential non-apoptotic mechanisms, we analyzed key autophagy-related proteins microtubule-associated protein 1 light chain 3 (LC3) and sequestosome 1 (SQSTM1, also called P62). LC3 exists in two forms: LC3-I, the cytosolic unlipidated form, and LC3-II, the lipidated form that associates with autophagosome membranes. The LC3-II/LC3-I ratio is commonly used to assess autophagosome formation and overall autophagic activity. P62 functions as an autophagic adaptor by binding ubiquitinated proteins and LC3-II, directing them to autophagic degradation. Under active autophagy, the LC3-II/LC3-I ratio increases, while P62 levels decrease.

Western blot analysis revealed that LFWE treatment increased the LC3-II/LC3-I ratio from 1 (control) to 2.11, 4.20, and 3.90 at 100, 200, and 400 μg mL^{-1}, respectively. Concurrently, P62 levels significantly decreased from 1 (control) to 0.43, 0.31, and 0.33 (Fig. 4). These results demonstrate a significant induction of autophagic activity by LFWE in H1975 cells, which may contribute to the observed growth suppression.

LFWE downregulates mutant EGFR through a lysosome-associated mechanism and suppresses downstream signaling

EGFR, particularly its activating mutations, is a clinically relevant therapeutic target in lung adenocarcinoma (Sharma *et al*. 2007). Conventionally, EGFR TKIs, such as erlotinib and gefitinib, suppress EGFR signaling by inhibiting kinase activity at the adenosine triphosphate (ATP)-binding site. However, H1975 cells harbor the EGFR L858R/T790M double mutation (Tang *et al*. 2008), which confers constitutive signaling and resistance to first-generation EGFR-TKIs by restoring ATP affinity and preventing effective kinase inhibition.

Given this therapeutic challenge, we investigated whether LFWE could modulate EGFR signaling in H1975 cells. We measured mutant EGFR protein levels and its downstream effectors, phosphorylated mammalian target of rapamycin (pmTOR) and phosphorylated AKT (pAKT). LFWE reduced mutant EGFR expression in a concentration-dependent manner, from 1 (control) to 0.86, 0.59, and 0.43 at 100, 200, and 400 μg mL^{-1}, respectively. pmTOR levels decreased from 1 to 0.74, 0.34, and 0.42, while pAKT decreased from 1 to 0.99, 0.86, and 0.62 across the same concentration series (Fig. 5A). At 200 and 400 μg mL^{-1}, mutant EGFR and pmTOR expression levels were significantly reduced, whereas pAKT showed a downward trend without reaching statistical significance (Fig. 5B). These results indicate that LFWE inhibits the mutant EGFR-mTOR axis, with a possible but not statistically confirmed impact on AKT signaling.

Since LFWE markedly reduced mutant EGFR protein expression, we next investigated whether this effect was associated with lysosome-mediated degradation. Treatment with the lysosomal inhibitor Bafilomycin A1 (BafA1) partially reversed the LFWE-induced decrease in EGFR levels, resulting in no significant difference between the LFWE and control groups (Fig. 6). This indicates that lysosomal activity may contribute to LFWE-mediated EGFR downregulation. Together with the observed activation of autophagic markers, the findings suggest that LFWE may promote lysosome-associated EGFR turnover, thereby attenuating oncogenic signaling in H1975 cells.

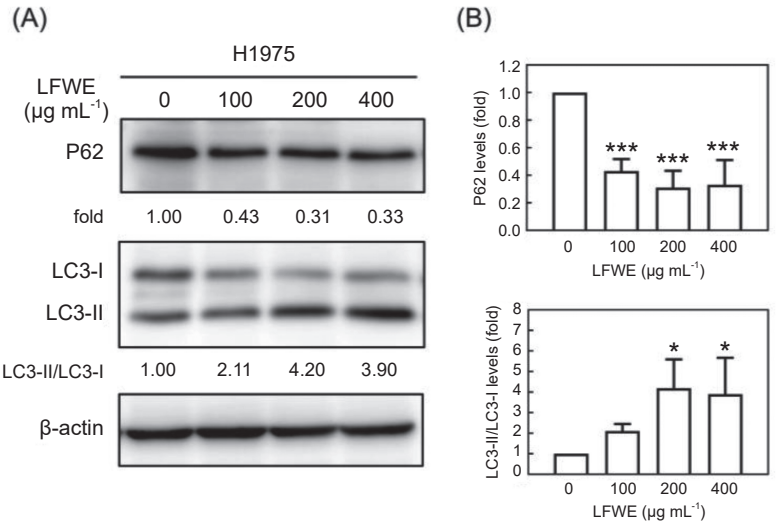


Fig. 4. Longan flower water extract (LFWE) induces autophagic response in H1975 lung adenocarcinoma cells. (A) H1975 cells were treated with LFWE (0–400 μg mL^{-1}) for 48 h, and levels of autophagy-related proteins (LC3-I/II, P62) were analyzed by Western blot. β-Actin served as a loading control. (B) The bar graphs show protein band intensities of LC3-I/II and P62, normalized to β-actin and expressed as fold change relative to 0 μg mL^{-1} (set as 1) at each LFWE concentration. Values are presented as mean ± *SD* (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test comparing each treatment group with the control (0 μg mL^{-1}). Significant differences are indicated ($^{*}P < 0.05$, $^{***}P < 0.001$).

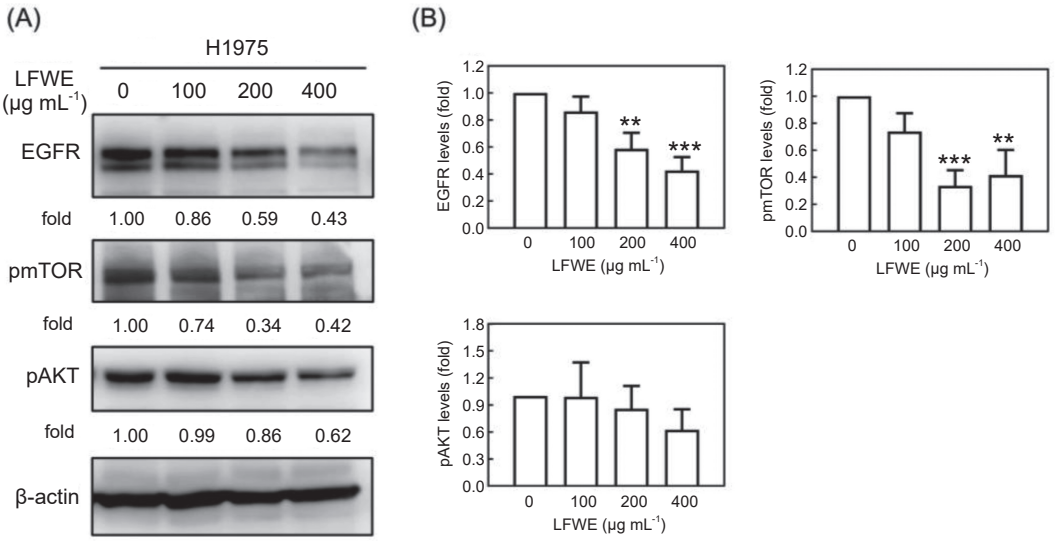


Fig. 5. Longan flower water extract (LFWE) inhibits mutant epidermal growth factor receptor (EGFR)-mediated signaling in H1975 lung adenocarcinoma cells. (A) H1975 cells were treated with LFWE (0–400 μg mL^{-1}) for 3 h, and protein levels of mutant EGFR and its downstream effectors (pmTOR, pAKT) were analyzed by Western blot. β-Actin served as a loading control. (B) The bar graphs show protein band intensities normalized to β-actin and expressed as fold change relative to 0 μg mL^{-1} (set as 1) for each protein. Values are presented as mean ± *SD* (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test comparing each treatment group with the control (0 μg mL^{-1}). Significant differences are indicated ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

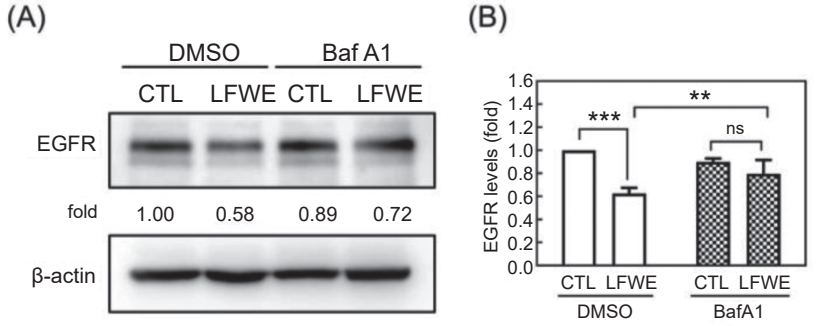


Fig. 6. Bafilomycin A1 attenuates LFWE (longan flower water extract)-induced degradation of mutant epidermal growth factor receptor (EGFR) in H1975 cells. (A) H1975 cells were pretreated with dimethyl sulfoxide (DMSO; vehicle) or Bafilomycin A1 (BafA1; 20 nM) for 30 min, followed by incubation with LFWE (200 μg mL^{-1}) for 3 h. Mutant EGFR levels were analyzed by Western blot, with β-actin serving as a loading control. (B) The bar graph shows quantified protein band intensities normalized to β-actin. Data represent mean ± *SD* (n = 3). Statistical significance was determined using Student's *t*-test to compare (i) control (CTL) vs. LFWE under DMSO, (ii) CTL vs. LFWE under BafA1, and (iii) LFWE (DMSO) vs. LFWE (BafA1). Significant differences are indicated (ns: non-significant, $^{**}P < 0.01$, $^{***}P < 0.001$).

CONCLUSION

LFWE exerts multiple anticancer effects in H1975 lung adenocarcinoma cells, including autophagy induction and lysosome-mediated mutant EGFR degradation, leading to inhibition of downstream mTOR and AKT signaling. However, LFWE exhibited a degree of toxicity toward non-malignant lung cells, and its apoptosis-inducing effect was modest. These limitations highlight the importance of further evaluating LFWE's safety and developing strategies to mitigate off-target effects in translational applications. Future studies should investigate whether low-dose LFWE in combination with conventional chemotherapeutics could enhance anticancer efficacy while reducing toxicity. In addition, isolating and characterizing its active components may provide safer and more potent anticancer agents. Together, these directions could broaden the translational potential of LFWE-based interventions against lung adenocarcinoma.

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龍眼花水萃物對肺腺癌細胞的抑制潛力與分子作用機制

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摘要

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肺腺癌是非小細胞肺癌中最常見的亞型，具有高發生率與低存活率。天然植物來源化合物提供了抗癌藥物開發的潛在來源。本研究探討龍眼花水萃物 (longan flower water extract; LFWE) 對 H1975 肺腺癌細胞的抑制作用及分子機制。LFWE 顯著降低 H1975 細胞存活率，並誘導明顯的形態變化。在機制方面，LFWE 激活自噬，表現為 LC3-II/LC3-I 比值增加與 P62 水平下降，並促進突變型表皮生長因子受體 (epidermal growth factor receptor; EGFR) 的溶酶體介導降解，進而抑制下游 mTOR 信號通路。然而，LFWE 對非惡性肺細胞亦有一些抑制效果，可能造成應用上的限制。進一步的安全性評估與轉化應用研究是必要的。總結來說，本研究提供初步證據，支持 LFWE 作為肺腺癌潛在治療策略的探索。

關鍵詞：龍眼花水萃物、肺腺癌、自噬、表皮生長因子受體 (EGFR)。

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