Impact of Phyllanthus emblica extract on A549 lung cancer cell malignancy via Akt/mTOR pathway

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Abstract: Objective: To investigate the effects of Phyllanthus emblicaextract on the malignant biological behaviors of human non-small cell lung cancer A549 cells via the protein kinase B/mammalian target of rapamycin (Akt/mTOR) signaling pathway. Methods: Human non-small cell lung cancer A549 cells were selected and divided into a control group (blank treatment), low-dose Phyllanthus emblicaextract group (50 μ g/mL), medium-dose group (100 μ g/mL), high-dose group (200 μg/mL), and a positive control group (100 nmol/L rapamycin). Cell Counting Kit-8 (CCK-8) assays and flow cytometry were performed to evaluate cell viability and apoptosis, respectively. Transwell assays and wound healing assays were utilized to assess cell invasion and migration capacities. Western blotting was employed to detect the protein expression levels of Akt, p-Akt, mTOR, and p-mTOR. Additionally, a mouse xenograft model was established using A549 cells from each group to monitor tumor growth dynamics and survival rates. Results: Compared with the control group, tumor volume and weight in the low-, medium-, and high-dose extract groups and the positive control group were significantly reduced in a dose-dependent manner (all $P< 0.05$). Furthermore, cell viability, invasive and migratory abilities, as well as the protein expression levels of p-Akt and p-mTOR in the extract-treated groups and the positive control group were significantly lower than those in the control group (all $P< 0.05$). These inhibitory effects were more pronounced in the positive control and high-dose groups compared to the medium-dose group, and in the medium-dose group compared to the low-dose group (all $P< 0.05$). Conversely, the apoptosis rate of A549 cells increased in the extract-treated groups in a dose-dependent manner (all $P< 0.05$). Conclusion: Phyllanthus emblicaextract inhibits the activity of the Akt/mTOR signaling pathway. This inhibition interferes with the invasion and migration of lung cancer A549 cells, suppresses subcutaneous tumorigenesis in nude mice, and induces cellular apoptosis.

Keywords: Phyllanthus emblicaextract, Akt/mTOR signaling pathway, Lung cancer, Invasion; Migration, Apoptosis

1. Introduction

Lung cancer is a solid malignant tumor characterized by high morbidity and mortality rates. Based on pathological features, it is classified into non-small cell lung cancer (NSCLC) and small cell lung cancer, with NSCLC accounting for over 80% of cases. The occurrence and progression of NSCLC are complex processes involving multiple factors, stages, and genes [1-2]. The protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is a classic cascade that is closely associated with apoptosis, cell cycle regulation, and other vital biological processes [3-4]. Studies have shown that the Akt/mTOR pathway can arrest the cell cycle of MCF-7 and A549 cells at the G2/M phase by regulating the expression of p-Akt and mTOR, ultimately inducing apoptosis [5].

Currently, the primary treatments for lung cancer include surgery, radiotherapy, and chemotherapy; however, these modalities are often limited by significant side effects and drug resistance, creating an urgent demand for novel antitumor agents that are both highly effective and low-risk [6]. Phyllanthus emblicaL. (commonly known as emblic leafflower), a member of the Euphorbiaceae family (Genus Phyllanthus), bears fruit that tastes sweet and sour with a slightly astringent aftertaste. It possesses remarkable medicinal value, traditionally used to clear heat, cool blood, promote digestion, strengthen the stomach, and relieve coughs. Additionally, it exhibits antioxidant, antibacterial, and anti-inflammatory properties [7-8]. Research

https://doi.org/10.62852/csa/2026/265

indicates that components of Phyllanthus emblicacan inhibit the synthesis of nitroso carcinogens, and their mechanisms are related to the modulation of cell cycles and carcinogen-related signaling pathways [9].

Based on this evidence, this study aims to investigate the effects of Phyllanthus emblicaextract on the malignant biological behaviors of lung cancer A549 cells via the Akt/mTOR signaling pathway. The results are reported as follows.

2. Materials and Methods

2.1. Experimental Materials

2.1.1. Experimental cells and animals

Human non-small cell lung cancer A549 cells were purchased from the Cell Bank of the Chinese Academy of Sciences. Seventy-five female BALB/c nude mice (Production License No. SYXK [Xiang] 2023-0007), aged 4 weeks and weighing 20–25 g, were obtained from Hunan Yi Ge Pharmaceutical Co., Ltd. Prior to the experiment, the mice were adaptively fed for one week under controlled environmental conditions: temperature maintained at 22–25°C, relative humidity at 45%–55%, and a 12-hour light/dark cycle. Food and water were provided ad libitum. This study was approved by the Animal Ethics Committee (Approval No. 2024LR-086).

2.1.2. Main reagents and instruments

Rapamycin was procured from Shanghai Wei Jin Biotechnology Co., Ltd. (Cat# IPA1021). RPMI-1640 medium was obtained from Shanghai Jing kang Bioengineering Co., Ltd. (Cat# OMDCM-031). The BCA Protein Assay Kit and Annexin V-FITC/PI Apoptosis Detection Kit were purchased from Shanghai Jing Ke Chemical Technology Co., Ltd. (Cat# JK-045-c, P-CA-201). Antibodies against phosphoinositide 3-kinase (PI3K), Akt, and mTOR were acquired from Wuhan Fine Biotech Co., Ltd. (Cat# GTX121937, FNab05417, YB22879). Antibodies specific for phosphorylated Akt (p-Akt), phosphorylated mTOR (p-mTOR), and phosphorylated 70 k Da ribosomal protein S6 kinase (p-p70S6K) were obtained from Shanghai Yubo Biotechnology Co., Ltd. (Cat# IC154412, IC194464, 85-86052-11). A FACS can flow cytometer (Beckman Coulter, USA), an optical microscope (Olympus, Japan), and a Model 680 microplate reader (Bio-Rad, USA) were used in this study.

2.1.3. Preparation of phyllanthus emblica extract

The extract was prepared via percolation using 95% ethanol. Briefly, 500 g of crushed Phyllanthus emblicafruits (passed through a 40-mesh sieve) were soaked in 95% ethanol (solid-liquid ratio 1∶8, v/w) for 24 h. Percolation was then conducted at a flow rate of 2 ml/min. The percolate was collected and concentrated via rotary evaporation (45°C, 0.08 MPa) until the ethanol odor was eliminated. The concentrate was subsequently subjected to vacuum freeze-drying (-50°C, 0.1 Pa) to obtain the crude extract powder. High-performance liquid chromatography (HPLC) analysis confirmed the quality of the extract (Column: Agilent ZORBAX SB-C18, 250 mm × 4.6 mm, 5 μ m; Mobile phase: methanol-0.1% phosphoric acid water gradient elution; Detection wavelength: 280 nm). The contents of ellagic acid (≥8.5%), luteolin (≥1.2%), and quercetin (≥0.9%) met the quality standards for experimental use.

2.2. Experimental Methods

2.2.1. Cell culture and grouping

A549 cells were incubated in Dulbecco's Modified Eagle Medium (DMEM) and subcultured when cell confluence reached 80%–90%. Cells were seeded into 24-well plates at a density of 5×10^4 cells/ml (5 replicates per group) and treated with various concentrations of the extract. The groups were defined as follows: Control group (untreated A549 cells), Positive control group (treated with 100 nmol/L rapamycin), and Low-, Medium-, and High-dose groups (treated with 50, 100, and 200 μ g/mL of Phyllanthus emblicaextract, respectively). The dosage regimen was referenced from Zhang et al. [15]. After incubation for 48 h, the supernatant was discarded, cells were resuspended in fresh medium, and collected for subsequent experiments.

https://doi.org/10.62852/csa/2026/265

2.2.2. Mouse xenograft model

Seventy-five mice were randomly divided into five groups (n= 15 per group). A549 cell suspensions from each experimental group were prepared and subcutaneously injected into the left axillary region of the mice (0.1 mL per mouse, containing 1.0×10^6 cells). Tumor volume was measured every three days, and survival status was recorded.

2.2.3. CCK-8 assay for cell viability

Cells from each group were adjusted to a density of 1.0×10^4 cells/ml and seeded into 96-well plates (100 μ L/well) for routine culture. Every 24 h, 10 μ L of CCK-8 solution was added to each well, followed by a 1-h incubation. The absorbance at 450 nm was measured using a microplate reader. The experiment was repeated three times, and the mean values were calculated to determine cell viability.

2.2.4. Flow cytometry analysis of apoptosis

A549 cell suspensions from each group were centrifuged at 1000 r/min for 5 min. The supernatant was discarded, and the cell pellet was washed twice with PBS to remove residual medium. Subsequently, 5 μ L of Annexin V/PI double-staining reagent (comprising 4 μ L Annexin V and 1 μ L PI) was added, followed by conventional incubation in the dark for 15 min. Finally, the cells were resuspended in 500 μ L of PBS and analyzed using a flow cytometer to assess apoptotic changes.

2.2.5. Transwell assay for cell invasion

Cell suspensions from each group were seeded into the upper chambers of Transwell inserts. The lower chambers were filled with 500 μ L of complete medium containing 10% FBS. After incubation at 37°C with 5% CO_2 for 24 h, the liquid in the upper chambers was removed. The cells on the upper surface of the membrane were gently wiped away with a cotton swab. The membranes were fixed with 4% paraformaldehyde for 30 min, washed with PBS, and stained with 0.1% crystal violet for 15 min. After rinsing off excess dye, five random fields of view were photographed under a microscope for cell counting.

2.2.6. Wound healing assay

A549 cell suspensions were seeded into 6-well plates at a density of 5.0×10^4 cells per well. Once the cells reached approximately 90% confluence, a sterile 200 μL pipette tip was used to create a straight scratch in the monolayer. Detached cells and debris were washed away with PBS, and the initial wound area was photographed. The cells were then cultured in a low-serum medium (2% FBS) for 24 h. The wound healing rate was observed and compared among groups under a microscope.

2.2.7. Western blotting

Total protein was extracted from A549 cells in each group. Protein concentration was determined using the BCA assay. Equal amounts of protein (20 μg per lane) were separated by SDS-PAGE and transferred onto PVDF membranes. The membranes were blocked with 10% goat serum for 2 h, washed, and then incubated with primary antibodies (diluted 1:500) overnight at 4°C. After washing, the membranes were incubated with secondary antibodies (diluted 1:500) at room temperature for 1 h. Following three washes, the protein bands were visualized using an enhanced chemiluminescence (ECL) kit. Images were captured, and protein expression levels were analyzed.

2.3. Statistical analysis

Statistical analyses were performed using SPSS software (version 23.0). Measurement data are expressed as the mean ± standard deviation ($\bar{x} \pm s$). Normality was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene's test. For data meeting the assumptions of normality and homogeneity, one-way analysis of variance (ANOVA) was used for comparisons among multiple groups, with the Student–Newman–Keuls (SNK-q) test applied for post-hoc pairwise comparisons. If the assumptions were violated, the Kruskal-Wallis H non-parametric test was used, followed by Dunn's test for pairwise comparisons. Count data are presented as [n (%)] and analyzed using the chi-square (χ) test. A two-tailed P-value < 0.05 was considered statistically significant.

https://doi.org/10.62852/csa/2026/265

3. Results

3.1. Comparison of tumor formation in mice

In the control group, 5 mice died and 10 survived. In the low-, medium-, and high-dose Phyllanthus emblicaextract groups, and the positive control group, the numbers of deaths were 4, 2, 1, and 1, respectively, with corresponding survival counts of 11, 13, 14, and 14 (χ=4.851, P=0.032). Compared with the control group, tumor volume and weight were significantly reduced in the extract-treated groups in a dose-dependent manner (all P<0.05, Table 1).

Table 1. Comparison of tumor formation among different groups ($\bar{x} \pm s$)

Groups	n	Tumor size (cm^3)	Tumor mass (g)
Ctrl	10	4.35±1.49	5.46±1.25
Low-dose group	11	4.20±1.81*	4.80±1.02*
Med-dose group	13	4.02±1.47*#	4.71±0.91*#
High-dose group	14	3.71±1.14*#△	4.15±0.85*#△
Rapamycin group	14	3.67±1.09*#△	4.15±0.90*#△

3.2. Comparison of A549 cell viability among groups

Compared with the control group, cell viability in the low-, medium-, and high-dose Phyllanthus emblicaextract groups, as well as the positive control group, was significantly decreased (all P< 0.05). Furthermore, cell viability in the high-dose extract group and the positive control group was significantly lower than that in the medium-dose group, which in turn was lower than that in the low-dose group (all P< 0.05, Table 2).

Table 2. Comparison of A549 cell viability among different groups (%)

Group	Cell viability		
	24h	48h	72h
Control group	100.02±6.07	100.31±6.12	100.10±6.04
Phyllanthus emblicaextract low-dose group	99.00±5.67	95.11±4.99*	87.00±4.12*
Phyllanthus emblicaextract medium-dose group	87.12±5.01	85.42±4.03*#	77.12±3.73*#
Phyllanthus emblicaextract high-dose group	82.57±4.72	73.01±3.75*#△	60.32±3.14*#△
Positive control group	82.60±4.65	72.97±3.71*#△	60.28±3.20*#△

3.3. Comparison of apoptosis rates among groups

Compared with the control group, the apoptosis rates in the low-, medium-, and high-dose Phyllanthus emblicaextract groups, as well as the positive control group, were significantly increased in a dose-dependent manner (all P< 0.05, Figure 1).

https://doi.org/10.62852/csa/2026/265

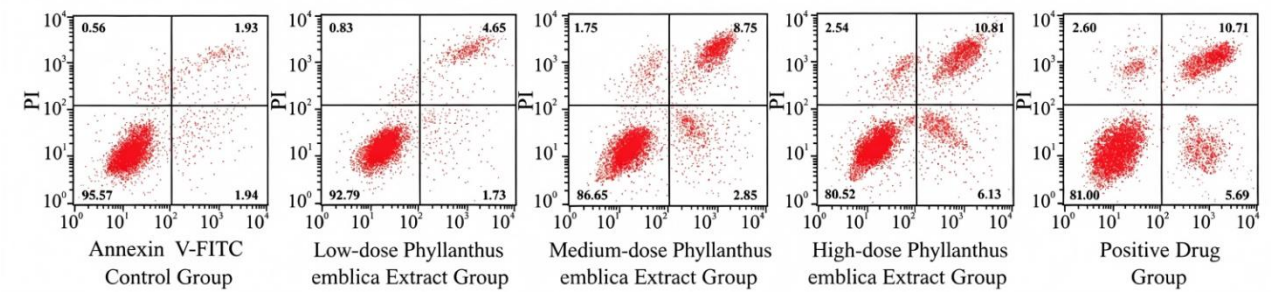

Figure 1. Comparison of apoptosis rates in A549 cells among different groups.

3.4. Comparison of invasion and migration abilities of A549 cells among groups

The invasive and migratory abilities of A549 cells in the low-, medium-, and high-dose Phyllanthus emblicaextract groups, as well as the positive control group, were significantly lower than those in the control group (all $P< 0.05$). Furthermore, these abilities in the positive control group and the high-dose group were significantly higher than those in the medium-dose group, which in turn were higher than those in the low-dose group (all $P< 0.05$, Table 3, Figure 2).

Table 3. Comparison of invasion and migration abilities of A549 cells among different groups ($\bar{x} \pm s$).

Group	Migration rate (%)	Invasive cell count
Control group	60.24±15.03	300.45±85.62
Phyllanthus emblicaextract low-dose group	48.67±13.12*	267.85±70.85*
Phyllanthus emblicaextract medium-dose group	36.75±12.04*#	190.42±50.73*#
Phyllanthus emblicaextract high-dose group	24.15±10.75*#△	156.10±40.01*#△
Positive control group	24.11±10.80*#△	156.05±39.91*#△

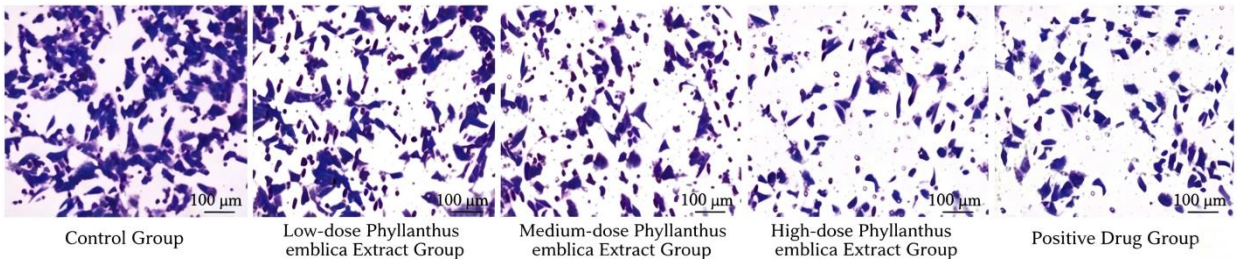

Figure 2. Comparison of invasive ability of A549 cells among different groups (Crystal violet staining).

3.5. Expression levels of PI3K/Akt/mTOR pathway proteins in A549 cells

The protein expression levels of PI3K, p-Akt, p-mTOR, and p-p70S6K in the low-, medium-, and high-dose Phyllanthus emblicaextract groups, as well as the positive control group, were significantly lower than those in the control group (all $P< 0.05$). Furthermore, the expression levels in the positive control group and the high-dose group were significantly lower than those in the medium-dose group, which in turn were lower than those in the low-dose group (all $P< 0.05$, Figure 3).

https://doi.org/10.62852/csa/2026/265

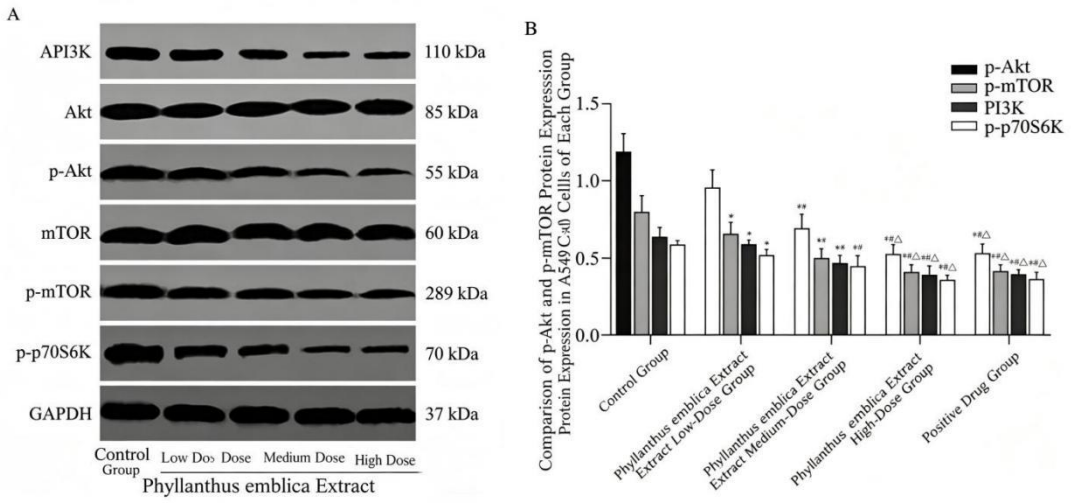

Figure 3. Expression levels of PI3K/Akt/mTOR pathway proteins in A549 cells.

4. Discussion

Lung cancer remains a prevalent and highly malignant tumor of the respiratory system. Current therapeutic strategies primarily rely on surgery, radiotherapy, and chemotherapy. However, limited by the inherent constraints of these modalities and their considerable toxic side effects, further improvements in clinical efficacy are challenging. Moreover, due to limitations in diagnostic capabilities, treatment accessibility, and uneven medical development, many patients are diagnosed at an advanced stage, thereby losing the opportunity for surgical intervention [10-11]. Therefore, there is an urgent need to identify novel antitumor agents that possess high efficacy and low toxicity. In recent years, the antitumor potential of Phyllanthus emblicaextract has garnered increasing attention [12-14].

Studies by Zhang et al. [15] demonstrated that Phyllanthus emblicaextract inhibits the proliferation, migration, and invasion of lung cancer cells by downregulating LINC01772 and subsequently upregulating miR-153 expression. Similarly, Li et al. [16] reported that different extracts of Phyllanthus emblicacombined with Reineckia carneasignificantly reduced tumor weight in Lewis lung carcinoma-bearing mice. Consistent with these findings, our study showed that treatment with low-, medium-, and high-dose Phyllanthus emblicaextract, as well as the positive control, significantly decreased the viability, invasive, and migratory abilities of A549 cells while increasing the apoptosis rate in a dose-dependent manner. Furthermore, in vivoexperiments revealed that the extract significantly reduced tumor volume and weight in a dose-dependent manner compared to the control group. These results confirm that Phyllanthus emblicaextract effectively suppresses the malignant biological behaviors of tumor cells.

Phytochemical analyses by Huang et al. [17] indicate that Phyllanthus emblicacontains flavonoids and minor phenolic acids, which exhibit multiple bioactivities including antioxidation, anti-aging, anticarcinogenesis, and immunomodulation. Among these, phenolic acids are considered the core substances responsible for its antitumor effects. Pharmacodynamic studies suggest that 95% and 70% ethanol extracts exhibit stronger inhibitory activities against tumor cell proliferation than aqueous extracts. Consequently, 95% ethanol percolation is recommended to achieve optimal utility.

The PI3K/Akt/mTOR signaling pathway is a hotspot in current tumor research and serves as a critical target for lung cancer therapy. Akt, a key molecule in this cascade, phosphorylates and activates downstream targets such as mTOR to induce cell growth and promote survival [18-19]. It has been reported that Akt phosphorylates GSK3β, leading to its inactivation and subsequent inhibition of cyclin D1 degradation. This results in the intracellular accumulation of cyclin D1, ultimately driving malignant cell proliferation [20]. Alternatively, Akt can phosphorylate mTOR and its downstream effectors, p70S6K

https://doi.org/10.62852/csa/2026/265

and 4E-BP1, thereby activating pro-survival signals and inhibiting p53-independent apoptosis, providing continuous support for tumor cell survival [21].

In the present study, we examined key nodes within this pathway, including upstream PI3K (a crucial activator of Akt) and downstream p70S6K (a direct substrate of mTOR). Our results demonstrated that the protein expression levels of PI3K, p-Akt, p-mTOR, and p-p70S6K were significantly downregulated in the extract-treated groups in a dose-dependent manner. This confirms that Phyllanthus emblicaextract inhibits the migration and invasion of A549 cells and promotes apoptosis, likely through the suppression of Akt/mTOR pathway activation. This mechanism may be attributed to the presence of polyphenolic compounds in the extract, such as ellagic acid, luteolin, and quercetin. Specifically, luteolin is superior in inhibiting tumor migration and invasion and can also suppress proliferation and induce cell cycle arrest. Beyond its gastroprotective, hypotensive, immunomodulatory, and anti-infective functions, quercetin exerts cytotoxicity against cancer cells via multiple molecular mechanisms. Additionally, high intake of kaempferol has been associated with a reduced incidence of various cancers and exhibits anti-angiogenic properties while protecting normal cell viability. We speculate that the synergistic action of these multiple polyphenolic components contributes to the suppression of malignant cancer progression [22-23].

5. Conclusion

Wang et al. [24] suggested that Phyllanthus emblicamay exert anti-hepatocellular carcinoma effects by targeting key molecules with high network connectivity and strong docking capabilities, such as Akt1 and MMP-9. The kinase domain of Akt1 directly phosphorylates the Ser2448 site of mTOR, enhancing the binding capacity of the mammalian target of rapamycin complex 1 (mTORC1) to its substrates and increasing the phosphorylation efficiency of downstream effectors by 3- to 5-fold. Cao et al. [25] noted that autophagy-related genes directly regulate the autophagic process, which is dynamically modulated by key pathways such as mTOR (nutrient signaling) and AMPK (energy signaling). As the core integrator of autophagic signals, mTORC1 positively or negatively regulates autophagy initiation in response to intracellular and extracellular stress stimuli. Their study found that eleutheroside B induced autophagy in lung cancer cells, potentially via the PI3K/Akt/mTOR signaling pathway.

However, our study did not specifically detect autophagy levels in lung cancer cells. Whether the inhibitory effect of Phyllanthus emblicaextract on the malignant progression of lung cancer is related to Akt/mTOR-mediated autophagy remains to be elucidated in future studies.

In summary, Phyllanthus emblicaextract inhibits the activity of the Akt/mTOR signaling pathway, thereby interfering with the invasion and migration of lung cancer A549 cells, suppressing subcutaneous tumorigenesis in nude mice, and inducing cellular apoptosis.

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