Tropical Journal of Pharmaceutical Research September 2022; 21 (9): 1859-1865
ISSN: 1596-5996 (print); 1596-9827 (electronic)
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Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i9.7

Original Research Article

Isoginkgetin inhibits lung cancer cell progression through miR-27a-5p/APEX1 axis

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Sent for review: 7 May 2022 *Revised accepted: 16 August 2022*

Abstract

Purpose: *To determine the influence of isoginkgetin on the progression of pulmonary carcinogenesis.*
Methods: *A549 cells exposed to isoginkgetin were transfected with miR-27a-5p mimetic and suppressor, as well as short hairpin RNA against apurinic/apyrimidinic endo-deoxyribonuclease 1 (sh-APEX1) for 24 h. Then, the proliferative, migration and invasive potential of A549 cells were determined using CCK-8, wound healing and Transwell assays, respectively. The association between miR-27a-5p and APEX1 was determined by dual-luciferase reporter assay.*
Results: *Isoginkgetin significantly suppressed A549 cell proliferative, migration and invasive activities ($p < 0.05$). Moreover, isoginkgetin significantly increased miR-27a-5p expression. Furthermore, miR-27a-5p suppressor annulled the influence of isoginkgetin on lung cancer progression. More importantly, the inhibitor directly targeted APEX1, and negatively modulated APEX1 expression ($p < 0.05$). However, APEX1 knockdown annulled the enhancing effect of miR-27a-5p inhibitor on A549 cell viability, migration and invasion ($p < 0.05$).*
Conclusion: *Isoginkgetin exerts an anti-lung cancer effect via miR-27a-5p/APEX1 axis. Thus, it is a potential therapy for the management of lung cancer; however, clinical studies are required to validate these findings of this study.*

Keywords: *Isoginkgetin, MiR-27a-5p, APEX1, Pulmonary tumor, Lung cancer*

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Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Pulmonary neoplasm is the most frequently diagnosed carcinoma worldwide, and it occupies the first position, both in new cancer cases and cancer-related deaths [1]. Early-stage lung cancer often presents no obvious symptoms. Since there are no obvious clinical features in the early stage, many cases are not diagnosed until the disease has advanced [2]. In addition, tumor cell migration and invasion are the main factors that affect the improvement of survival rate after lung cancer treatment [3]. Therefore, it is very important to identify and develop new anti-tumor drugs that inhibit lung cancer metastasis.

Several achievements have been made in the research and development of traditional Chinese medicines with anti-cancer potential [4]. However, at present, most of the studies are based on compound therapy. Although

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traditional Chinese medicines produce curative effects, the mechanisms involved in the use of traditional Chinese medicines for treating lung cancer are intricate. This limits their clinical application and promotion.

Ginkgo biloba is a traditional Chinese medicine which has been used for treating several cancers in China for thousands of years [5]. Evidence has shown that Ginkgo biloba exocarp extracts suppressed lung cancer growth and metastasis through induction of apoptosis and autophagy, and suppression of angiogenesis [6]. Isoginkgetin belongs to a family of flavonoids extracted from Ginkgo biloba leaves, and it exerts a variety of pleiotropic and pharmacological actions, including anti-cancer and anti-inflammatory effects [7]. However, the influence of isoginkgetin on pulmonary neoplasm has not been reported. The present research was focused on understanding the influence of isoginkgetin on growth, migration and spread of pulmonary carcinoma cells.

EXPERIMENTAL

Cell culture

Cancerous A549 cells and BEAS-2B obtained from ATCC, USA, were maintained in F-12K and RPMI-1640 medium (ATCC, USA) containing 10 % FBS (Invitrogen, USA) in humidified 5 % CO_2 chamber at 37 ^oC.

Cell treatment and transfection

To determine the effect of isoginkgetin on cell viability, graded doses of isoginkgetin (Thermo Fisher Scientific, USA) were applied in treating A549 cells for 24 h.

For knockdown of APEX1 expression, short hairpin RNAs (shRNAs) against APEX1 (sh-APEX1) and corresponding control (sh-NC), and microRNA-27a-5p mimic and suppressor were bought from Genepharma (Jiangsu, China). The sequences for cell transfection are listed in Table 1. When A549 cells grew to 70 % confluence, the cells were transfected with 100 nM NC mimetic, NC blocker, miR-27a-5p mimetic, miR-27a-5p blocker, sh-NC or sh-APEX1 for 24 h, with Lipofectamine 2000.

CCK-8 assay

Following plating of A549 cells for 72 h and 2-h incubation with CCK-8 solution (Beyotime, China), OD was read at 490 nm in a spectrophotometer (Bio-Rad, China).

Wound healing studies

The A549 cells were seeded at a density of 5 × 10^5 cells /well in 6-well plates. When the cells grew to 85 % confluence, a wound was made on the surface of the cells with a 200-μL sterile pipette tip (Axygen, USA). Then, the A549 cells were cultured without FBS for 48 h. The distance between both sides of the wound was recorded using an inverted microscope.

Transwell assay

In migration assay, A549 cells were plated in upper transwell chamber, and cultured in F-12K medium (ATCC, USA) without FBS. In invasion assay, A549 cells were plated in upper transwell compartment pre-surfaced with Matrigel. The lower transwell chamber contained F-12K medium (ATCC, USA) with 20 % FBS (Invitrogen, USA). Forty-eight hours later, the migrated and invaded cells were subjected to fixation in 4 % ρ-HCHO, and were stained using crystal violet (0.1 %).

Dual-luciferase reporter assay

The binding sites of 3'-UTR of APEX1 were mutated from 5'-UUU GAG CCU GGG AAA UAA GCC CC-3' to 5'-UUU GAG CCU GGG AAA AUU CGG GC-3'. The wild-type and mutated sequences of APEX1 were cloned into pGL3-Firefly-Renilla vector so as to construct APEX1 wild-type (APEX1-WT), APEX1 mutant (APEX1-MUT) Firefly-Renilla reporter plasmids. Then, following 24-h co-transfection of A549 cells using 0.5 μg pGL3-Firefly-Renilla vector and 100 pmol mimic or inhibitor, luciferase was assayed with Promega kits.

Table 1: Sequences for transfection

Gene	**Sequences** (5′-3′)
sh-APEX1	GACACGCGACUUGUACCAC
sh-NC	UCUAUGUGUCUUAAUCCCUUGUCCU
miR-27a-5p mimetic	AGGGCUUAGCUGCUUGUGAGCA
miR-27a-5p blocker	UGCUCACAAGCAGCUAAGCCCU
NC mimetic	UUUGUACUACACAAAAGUACUG
NC inhibitor	CAGUCCUUUUGUGUAGUACAA

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

Total RNA extraction from A549 cells was done with TRIzol. Then, the RNA was subjected to reverse-transcription to yield cDNA, followed by RT-qPCR assay with PCR kit (Qiagen, Germany). Relative expressions of genes were evaluated using the $2^{-\Delta\Delta Ct}$ procedure. The internal standards were U6 and GAPDH. Table 2 shows the primers used in qRT-PCR.

Immunoblot assay

Total proteins were isolated from A549 cells with RIPA buffer, and protein levels in samples were measured with BCA method. Then, the protein samples were subjected to 10 % SDS-PAGE, followed by transfer to PVDF membranes. Following membrane blocking with non-fat milk, the protein bands were subjected to 12-h incubation with 1° antibodies for APEX1 (1:1000, ab189474, Abcam, USA) and GAPDH (1:5000, ab8245, Abcam, China) at 4 °C. Thereafter, the protein bands were incubated for 60 min with the related secondary antibodies, followed by visualization with ECL, and semi-quantification with ImageJ software. The internal reference was GAPDH.

Statistics

Data were analyzed with Prism GraphPad 5.0 and presented as mean ± SD. Statistically significant variations between two groups were assessed using *t*-test (two-tailed), while 1-way ANOVA and Tukey's post hoc test were employed for multi-group comparisons. Values of $p < 0.05$ were considered indicative of statistical significance.

RESULTS

Isoginkgetin suppressed cell proliferation and metastasis

Isoginkgetin treatment suppressed A549 cell proliferation, with 20 μM isoginkgetin producing the largest effect (Figure 1 A). Compared to the control group, 20 μM isoginkgetin group had marked inhibition of A549 cell migration (Figure 1 B and C). Transwell assay revealed that, compared to the control group, 20 μM isoginkgetin group had marked suppression of migratory and invasive potential of A549 cells (Figure 1 D and E). The aforementioned results showed that isoginkgetin suppressed the worsening of lung cancer.

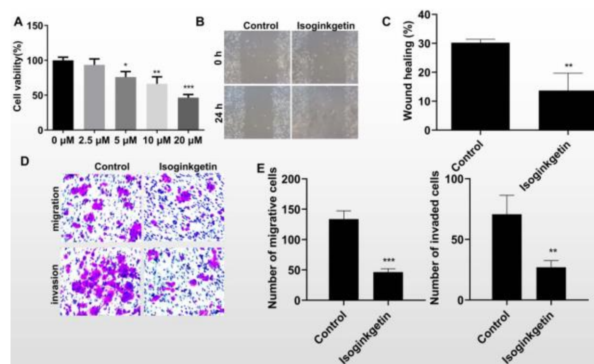

Figure 1: Isoginkgetin inhibited lung cancer cell proliferation and metastasis. A549 cells were treated with 2.5, 5, 10, and 20 μM isoginkgetin for 24 h. (A) Growth of A549 cells, as assayed using CCK-8 assay. (B & C) Migration of A594 lung cancer cells, as measured using wound healing assay. (D - E) Cell migrative and invasive potential. *P* < 0.05*, < 0.01**, < 0.001***, relative to control

Isoginkgetin inhibited lung carcinoma cell growth and metastasis by enhancing miR-27a-5p expression

An important target of traditional Chinese medicine is miRNA [8]. Therefore, this study determined whether isoginkgetin regulated lung cancer cell malignancy through regulation of miR-27a-5p. The results from RT-qPCR assay showed that, compared to lung epithelial cell line BEAS-2B, miR-27a-5p level was significantly decreased in pulmonary cancer cell line A549. Moreover, compared to untreated A549 group, isoginkgetin treatment suppressed miR-27a-5p level in A540 cells (Figure 2 A). Relative to control, there was significantly suppressed A549 cell viability in isoginkgetin + NC inhibitor group.

Table 2: Primers used in PCR

Gene	5′-3′	5′-3′
miR-27a-5p	GCGGCGGAGGGCTAGCTGCTTG	ATCCAGTGCAGGGTCCGAGG
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT
APEX1	AGTAAGACGGCCGCAAAGAA	TTGCCACTGGGTGAGGTTTT
CLEC4E	CAACTCACAGGAGGAGCAGG	AGCTATGTTGTTGGGCTCCC
FSD2	AGCGACACTCACTTCACCAG	AGGAGAGGCAATTTGCTCCC
TMEM199	AACCCAGAACTAGTTGCCCG	CAGCAACCACCGTGACAATG
GAPDH	GTCAAGGCTGAGAACGGGAA	AAATGAGCCCCAGCCTTCTC

In addition, relative to isoginkgetin + NC inhibitor group, isoginkgetin + miR-27a-5p inhibitor group had enhanced A549 cell viability (Figure 2 B). Moreover, miR-27a-5p inhibitor reversed the inhibitory influence of isoginkgetin on the migratory and invasive potential of A549 cells (Figure 2 C–F). Overall, isoginkgetin suppressed the deterioration of lung cancer through up-regulation of miR-27a-5p.

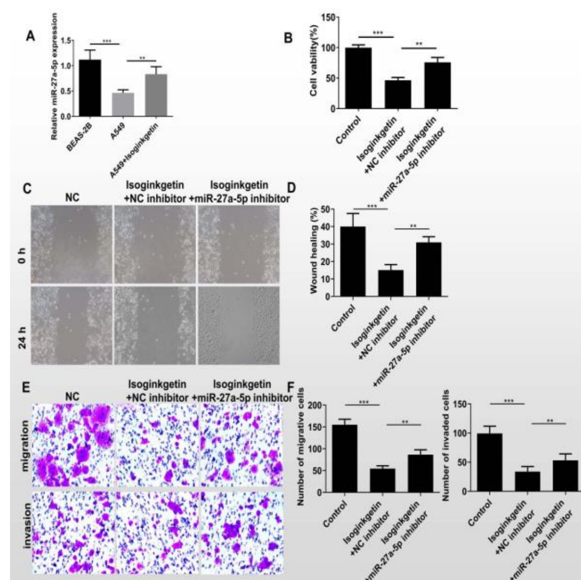

Figure 2: Isoginkgetin inhibited lung cancer cell proliferation and metastasis by up-regulating miR-27a-5p expression. (A) Levels of miR-27a-5p in BEAS-2B, A549, and A549 + isoginkgetin groups. A549 cells exposed to 20 μM isoginkgetin were transfected with miR-27a-5p inhibitor for 24 h. **(B)**. Lung cancer cell viability. **(C & D)** Migration of lung cancer cells, as determined using wound healing measurement. **(E F)** Migratory and invasive potential of A549 cells. *P* < 0.05*, < 0.01**, < 0.001***, compared to BEAS-2B, control group and the isoginkgetin + NC inhibitor group, respectively

MiR-27a-5p directly targeted APEX1 in lung cancer

Online databases miRDB, TargetScan and miRTarbase were employed for determination of intersecting target genes. Venn diagram showed 4 common elements (APEX1, CLEC4E, FSD2 and TMEM199) in online databases (Figure 3 A). The results of qRT-PCR assay showed that APEX1 level in A549 cells was up-regulated, while isoginkgetin decreased APEX1 level, but had no effects on the expressions of CLEC4E, FSD2 and TMEM199 (Figure 3 B).

Therefore, APEX1 was predicted as the potential focus of miR-27a-5p. Its points of interaction with miR-27a-5p are displayed in Figure 3 C. The miR-27a-5p mimetic suppressed luciferase of APEX1 WT. However, it had no effect on APEX1 MUT (Figure 3 D). Furthermore, its mimetic significantly decreased APEX1 level, but its inhibitor up-regulated APEX1 expression (Figures 3 E - F**)**. Above all, miR-27a-5p negatively modulated APEX1 expression by binding to it.

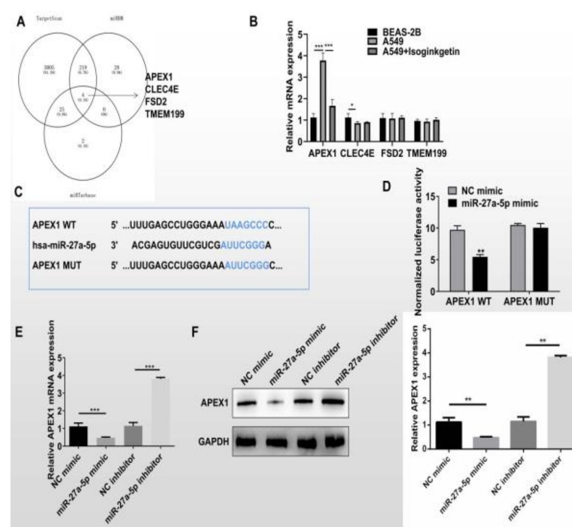

Figure 3: miR-27a-5p directly targeted APEX1 in lung cancer. (A) Online databases employed for prediction of intersecting focal genes. (B) The mRNA levels of APEX1, CLEC4E, FSD2 and TMEM199, as determined using PCR. **(C)** Predicted interaction locations for miR-27a-5p and APEX1. (D) Association of miR-27a-5p with APEX1. **(E)** The APEX1 mRNA level in A549 cells was evaluated via RT-qPCR assay. **(F)** The APEX1 protein level in A549 cells, as measured using immunoblot assay. *P* < 0.05*, < 0.01**, < 0.001***, vs BEAS-2B group, A549 group, and NC mimic or NC inhibitor group, respectively

Isoginkgetin inhibited the proliferative and metastatic activities of A549 cells via the miR-27a-5p/APEX1 route

In order to determine whether isoginkgetin regulated lung cancer cell progression through miR-27a-5p/APEX1 route, cells were exposed to isoginkgetin and subjected to co-transfection with miR-27a-5p inhibitor and sh-APEX1 for 24 h. The inhibitor suppressed APEX1 expression, but knockdown of APEX1 increased APEX1 expression (Figure 4 A).

Functionally, knockdown of APEX1 reversed the miR-27a-5p inhibitor-induced enhancement of proliferative and invasive potential of A549 cells (Figures 4 B - F). Collectively, these data suggest that isoginkgetin suppressed lung carcinoma proliferation and metastasis through the miR-27a-5p/APEX1 axis.

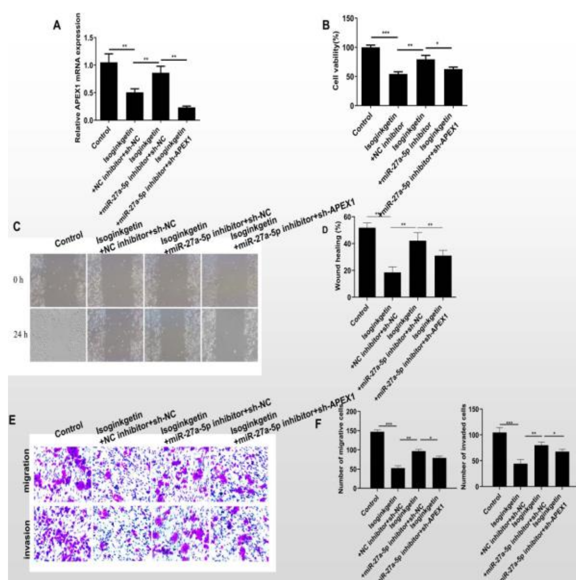

Figure 4: Isoginkgetin inhibited the growth and metastatic potential of lung cancer cells through the miR-27a-5p/APEX1 route. A549 cells exposed to isoginkgetin were subjected to co-transfection with miR-27a-5p inhibitor and sh-APEX1 for 24 h. **(A)** The level of APEX1 mRNA in A549 cells. **(B)**. Viability of A549 lung cancer cells. **(C & D)** Migration of A549 lung cancer cells. **(E & F)** Migratory and invasive potential of A549 cells. $P < 0.05^*$, $< 0.01^{**}$, $< 0.001^{***}$, vs. control, isoginkgetin + NC inhibitor + sh-NC group, and isoginkgetin + miR-27a-5p inhibitor + sh-NC group, respectively

DISCUSSION

Although significant advances have been made in lung cancer therapy, including surgery, radiotherapy, chemotherapy, molecular targeting and immunotherapy, the prognosis of lung cancer still remains poor [9]. Chemotherapy drugs are expensive and have very toxic side effects. In contrast, traditional Chinese medicines have the advantages of multiple targets, low toxic side effects, wide sources and reliable effects, and they are often used as adjuvant therapies for lung cancer [3].

The effects produced by monomers and derivatives of natural Chinese medicine in the prevention of lung cancer are gradually being recognized [10]. For instance, Lin *et al* found that resveratrol from the traditional Chinese medicine *Polygonum cuspidatum* increased the chemosensitivity of lung cells to cisplatin, and suppressed lung cancer progression through reduction in MUC5AC level [10]. Thus, it is crucial to study the molecular bases associated with the anti-cancer effects of bioactive components of traditional Chinese medicines. One of the fundamental measures for suppressing the incidence and spread of tumors involves controlling the growth, spread and invasion of lung carcinoma cells [11].

Isoginkgetin exerts anti-cancer and anti-inflammation properties [12,13]. For instance, Yoon *et al* reported that isoginkgetin inhibited human fibrosarcoma cell growth by regulating the PI3K/Akt-dependent MMP-9 expression [12]. Besides, Tsalikis *et al* found that isoginkgetin sensitized cancer cells to apoptosis by disrupting lysosomal homeostasis and impairing protein clearance [13]. It has been reported that isoginkgetin enhanced immune-protective response against tumor antigens [14]. In the present study, isoginkgetin suppressed the deterioration of lung cancer. The miRNAs comprise small, highly conserved non-coding RNAs which bind to the 3'-UTR area of downstream mRNAs [15]. Many miRNAs with abnormal expressions in lung cancer participate in the occurrence and spread of lung cancer. It is well known that miRNA is an important target of traditional Chinese medicine [16]. High throughput sequencing has revealed several abnormally expressed miRNAs in curcumin-treated lung cancer cells [16]. Therefore, the development of drugs targeting miRNAs is promising for the treatment of lung cancer through regulation of miRNA expressions. Studies have revealed that miR-27a-5p is down-regulated in pulmonary neoplasms, a finding which suggests that it might be a promising biomarker for early diagnosis [17]. Furthermore, it has properties of a tumor suppressor gene: its overexpression significantly reduced the proliferation of pulmonary carcinoma cells [17]. In this work, the expression of miR-27a-5p was increased by isoginkgetin, but miR-27a-5p blocker reversed the inhibitory influence of isoginkgetin on lung cancer progression. These results indicate that miR-27a-5p is a potential target for isoginkgetin. The use of online databases for analysis of intersecting target genes revealed that miR-27a-5p directly targeted APEX1 and negatively modulated APEX1 expression. Apurinc/Apyrimidinic Endo nuclease 1 (APEX1) is associated with DNA damage response and redox reaction [18]. Inhibition of APEX1 expedited DNA damage response in lung cancer [18]. Previous studies demonstrated that APEX1 was abnormally expressed in a variety of tumors, and was associated with the pathogenesis of cancers [19, 20]. For instance, Huang et al found that APEX1 level was increased in melanoma, and APEX1 overexpression enhanced the development of melanoma [19]. Wang et al showed that miR-296-3p inhibited lung cancer progression through down-regulation of APEX1 [20]. This research has demonstrated that APEX1 knockdown

blocked miR-27a-5p suppressor-induced enhancement of the proliferative, migratory and invasive potential of the cells.

CONCLUSION

Isoginkgetin regulates miR-27a-5p/APEX1 axis, thereby suppressing lung cancer growth and metastasis. This finding indicates that miR-27a-5p/APEX1 axis may be an effective target for lung cancer treatment, thus providing a potential strategy for the treatment of lung cancer.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Langjie Wu conceived and designed the study, and drafted the manuscript. Langjie Wu and Li Xu collected, analyzed and interpreted the experimental data. Li Xu revised the manuscript for important intellectual contents. Both authors read and approved the final manuscript.

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