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Cell Lung Cancer Proliferation Downregulation by Tanshinone IIA: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: The current investigation was carried out to ascertain the efficacy of Tan IIA in treating both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Material and methods: To obtain documentation and scientific evidence for the effectiveness of Tan IIA on small cell lung cancer cells articles published in international databases such as PubMed, Web of Science, Scopus, Sites Direct, Elsevier, Wiley, and the search engine Google Scholar were used. Data were analyzed using STATA software, version 17. Effect size with 95% confidence interval (CI), random effects model, and REML method were used.

Results: Seven studies were examined. Tanshinone IIA treatment downregulated SCLC proliferation by 4.8 percent (ES: 4.8 95 percent CI -0 point61, 1 point56). Results indicate that Tanshinone IIA treatment decreased NSCLC cell migration (ES: 6.2 percent, 95 percent confidence interval [CI], 1.01).

Conclusions: According to the current study, tanshinone IIA can inhibit the growth of both SCLC and NSCLC. Therefore, it may be regarded as a therapeutic option for both.

1. Introduction

The most deadly cancer in the world for both male and female patients, lung cancer is extremely aggressive, frequently metastasizes quickly, and is common.[1] Nowadays, stages III and IV of the disease are present in about 70% of patients with a diagnosis of lung cancer.[2] Lung cancer continues to be the most common cause of cancer-related death, accounting for 1 point 8 million deaths (18%) in 2020, according to the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 cancer incidence and mortality estimates.[3] According to projections, the number of lung cancer deaths in men will be between 1 and 6 million and in women between 1 and 8 million by 2040.[4] The field's recent advances notwithstanding, survival rates have not increased over the previous thirty years, but they have decreased. This is primarily because of the shortcomings in the strategies for diagnosis and treatment.[5] Considering that lung cancer is a deadly and nearly incurable cancer, any effort to increase the survival rate of these patients, even for a few months, may be worthwhile.[6] Small cell lung cancer (SCLC), which accounts for 15-20% of lung cancers, has a 5-year survival rate of less than 6% and is therefore considered the most malignant and deadly form of lung cancer.[7] Standard first-line treatments include a combination of etoposide and platinum-based chemotherapy. Because this treatment is limited, most SCLC patients experience relapse and metastasis.[8] Therefore, the use of new therapeutics is very important. Studies have shown that herbal remedies, particularly Chinese herbal medicine and its extracts, have shown good efficacy with low toxicity in treating multiple tumors in clinical practice.[9] Study results suggest that the overall survival of SCLC patients is improved by Chinese herbal medicine.[10, 11] For Inver, studying active ingredients derived from Chinese plants for treating SCLC is very important and can be considered promising. Tanshinone IIA (Tan IIA) is an extracted compound with antitumor activity.[11-14] However, studying the underlying molecular mechanism is challenging and not widely accepted worldwide. Tanshinone

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IIA is one of the main active ingredients of Salvia miltiorrhiza, whose antioxidant, anti-inflammatory, and neuroprotective effects have been proven in studies.[15, 16] Studies have demonstrated the antitumor effect of Tanshinone IIA in various cancers, but its antitumor effect on SCLC is not yet fully understood and remains challenging.[14] Therefore, a study that examines the results of existing studies and presents evidence through synthesis is very important. Therefore, the present study aimed to determine the efficacy of Tanshinone IIA SCLC and NSCLC.

2. Material and methods

Search strategy and data sources

To obtain documentation and scientific evidence for the effectiveness of Tanshinone IIA on small cell lung cancer cells, articles published in international databases such as PubMed, Web of Science, Scopus, Sites Direct, Elsevier, Wiley, and the search engine Google Scholar were used. The search process in these databases was carried out using the keywords lung cancer, lung Neoplasms, lung Tumors, small cell lung cancer cells, Small-cell lung cancer, small cell lung carcinoma, metastasis, drug resistance, Tanshinone IIA, anti-tumor activity, and medical subject headings (MeSH) terms were also used, which included (((((((("Lung Neoplasms"[Mesh]) OR ("Lung Neoplasms/classification"[Mesh] OR "Lung Neoplasms/therapy"[Mesh])) OR "Small Cell Lung Carcinoma"[Mesh]) OR ("Small Cell Lung Carcinoma/prevention and control"[Mesh] OR "Small Cell Lung Carcinoma/therapy"[Mesh])) OR "Neoplasm Metastasis"[Mesh]) AND "Drug Resistance"[Mesh]) AND "Salvia miltiorrhiza"[Mesh]) OR "tanshinone II A sodium sulfonate" [Supplementary Concept].

In addition, the reference list of procured items was reviewed to identify the used items that were not procured using the above methods. All articles were selected based on inclusion criteria and the PICOS strategy.

Inclusion and exclusion criteria

Inclusion criteria included: small cell lung cancer cells (P: population); Tanshinone IIA (I: Interventions); Studies with or without a control group (C: comparison); Studies that reported outcomes such as small cell lung cancer cell proliferation and migration (O: result); All randomized clinical trials, animal studies, in vitro and in vivo studies (S: studies). Excluded from the study were studies published in languages other than English, review studies and books, qualitative studies, studies without complete results, and scientific sources without full text.

Selection and data collection process

A form developed based on the research purpose was used for data extraction. This form contained sections such as first author's name, year, lung cancer types, sample size, study groups, Tanshinone IIA group, control group, cell and in vitro treated cells of the study. Two independent authors, Koror and the third, checked the data separately and evaluated the completed form. All articles were entered into the End. Note X.8 software and the full text of the articles were reviewed by two independent authors. Any disagreements between the two authors were resolved through discussion, and a third reviewer was consulted when necessary.

Statistical analysis

Version 17 of STATA was used to analyze the data. I^2 values representing 25%, 50%, and 75% of small, medium, and large amounts of heterogeneity were obtained using the I^2 index and P value <0.1 for the Q test, which was used to assess the heterogeneity of the studies. We applied the random effects model, REML method, and effect size with a 95 percent confidence interval (CI). We used the Egger test to verify publication bias.

3. Results

Study selection

The first search turned up 291 articles. Initially, it was discovered by reading the article titles that 61 articles had been deleted because they were duplicates. In the subsequent phase, 190 articles that did not pertain to the current study's goals were eliminated from consideration by reviewing the abstracts of the 208 articles by the inclusion and exclusion criteria. During the third stage, 11 articles were eliminated based on insufficient, irrelevant, or inconsistent data with the goals, following a thorough review of the complete texts of the remaining 18 articles. In the end, this study made use of seven publications.

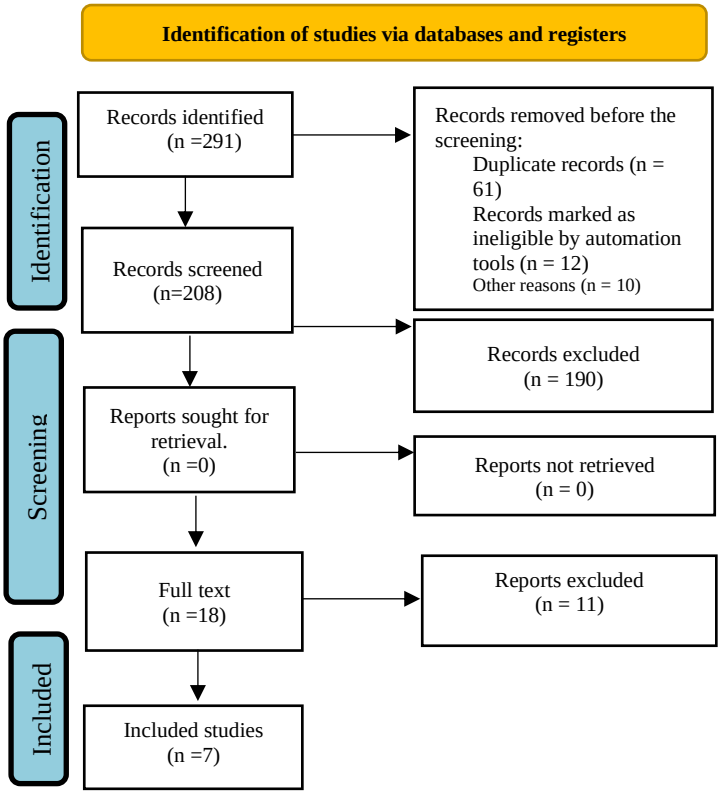

Fig. 1. PRISMA 2020 Checklist.

Effects of Tanshinone IIA treatment on Cell lung cancer proliferation downregulation

Small cell lung cancer

There was minimal inter-study heterogeneity (I^2=0; p=0.86) and a 4.8% (ES: 4.8, 95 percent CI -0.61, 1.56) down-regulation of SCLC proliferation following Tanshinone IIA treatment (Q=0.03) in Fig. 2. These findings show that Tanshinone IIA treatment decreased SCLC cell migration by inhibiting various processes, including EMT.

Non-small cell lung cancer

There was minimal inter-study heterogeneity (I^2=0; p=0.89) and a 6.2% (ES: 6.2%, 95 percent CI 0.23, 1.01) down-regulation of NSCLC proliferation following Tanshinone IIA treatment. Q=1.15) in Fig. 3. These findings suggest that Tanshinone IIA treatment inhibited NSCLC cell migration.

Study characteristics

Table 1 outlines the approaches and procedures used in the studies. Some of the studies studied cells similarly, but the cells' in vitro treatment duration was consistent across all of them.

Publish bias

Based on Fig. 4, it can be concluded that bias was not present in the studies included in the meta-analysis because the data in the funnel plot did not disperse.

Table 1. Characteristics of included studies.

Study. Years	Types of Lung Cancer	Sample Size	Study Groups	Tanshinone IIA Group	Control Group	Cells	Cells Treated in Vitro
Jiang et al., 2024[17]	SCLC	10 Male BALB/nude mice	Tanshinone IIA (n = 5) Control (n = 5)	Intraperitoneal injection of 10 mg/kg Tanshinone IIA every other day	10 mg/kg of saline	H1688, H446, BEAS-2B and HBE cells	Tanshinone IIA (0, 1, 2, 4, or 6 μM) for 24, 48, or 72 h.
Qi et al., 2022 [18]	NSCLC	12 male BALB/c-nu/nu nude male mice	Tanshinone IIA (n = 6) Control (n = 6)	Tanshinone IIA (20 mg/kg) intraperitoneally every day for two weeks	Saline	Human NSCLC A549 and H292 cell lines	Tanshinone IIA (0, 1, 2 and 4 μM) or LY294002 (10 μM) for 24, 48, 72 h
Bai et al., 2022 [19]	NSCLC	Nude BALB/c mice	NR	20 mg·kg−1 for Tan IIA	Vehicle control	A549, PC-9, HCC827, and H1975	Tanshinone IIA (0, 1, 2 and 4 μM) or LY294002 (10 μM) for 24, 48, 72 h
Gao et al., 2020[20]	NSCLC	6-week-old female athymic nude mice	Tanshinone IIA and Control	Intraperitoneal injection of 10 mg/kg Tanshinone IIA daily	Vehicle control	HCC827, H1975, and A549	Tanshinone IIA (0, 1, 2 and 4 μM) or LY294002 (10 μM) for 24, 48, 72 h
Xie et al., 2015 [21]	NSCLC	-----	Tanshinone IIA and Control	-----	-----	A549	Tanshinone IIA (2.5−80 μmol/L) for 24, 48 and 72 h
Zhang et al., 2014[22]	NSCLC	-----	-----	-----	-----	A549	Tanshinone IIA (2.5−80 μmol/L) for 24, 48 and 72 h
Cheng et al., 2010[23]	SCLC	----	-----	-----	-----	H146 cells	Tanshinone IIA (2.5−80 μmol/L) for 24, 48 and 72 h

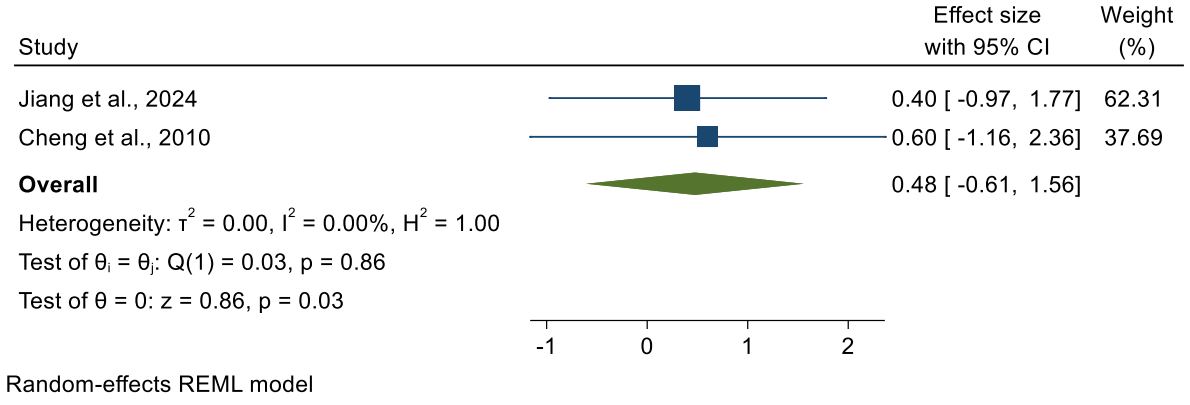

Fig. 2. Forest plot showed the effects of Tanshinone IIA treatment on SCLC proliferation.

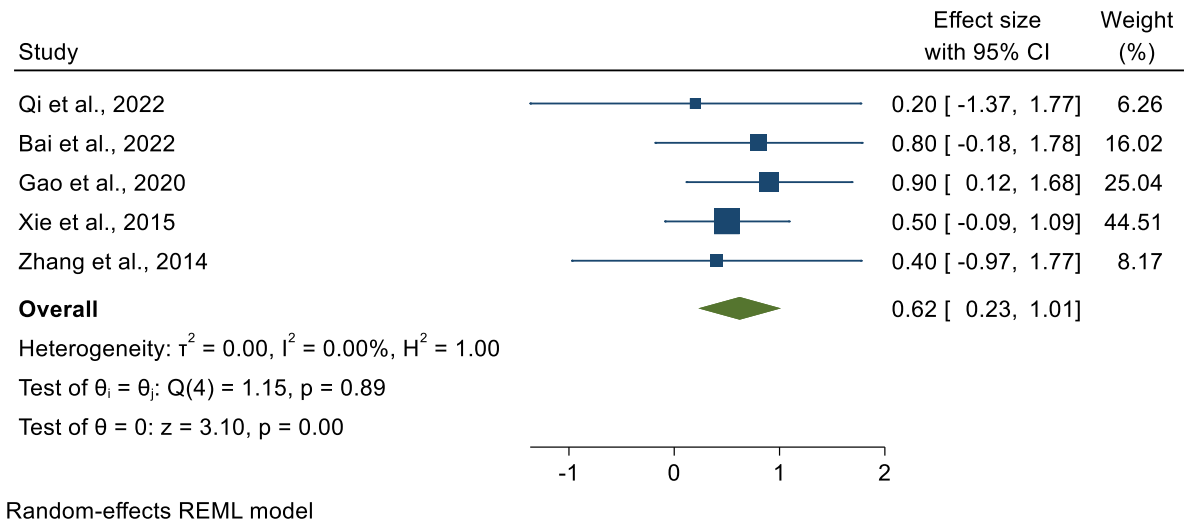

Fig. 3. Forest plot showed the effects of Tanshinone IIA treatment on NSCLC proliferation.

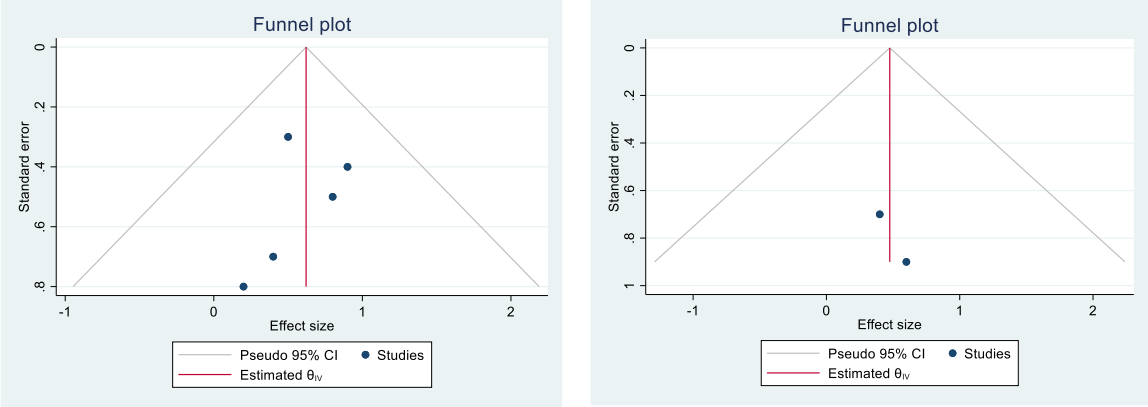

Fig. 4. The funnel plot showed the relationship between a study's effect size and precision.

4. Discussion

This study presents the first meta-analysis that we are aware of that looks at tanshinone IIA's ability to slow down the growth of lung cancer cells. According to the searches, just seven articles were found overall, with two discussing SCLC. Given the available data, neuroendocrine-derived SCLC is an aggressive form of the disease with a rapid course and a metastasis rate of over 50% in most cases.[24] While initial chemotherapy and radiation therapy response rates are adequate, the majority of these patients have advanced stages of their illnesses.[25] Thus, one section of this study examined the impact of Tanshinone IIA treatment on SCLC proliferation to offer a fresh approach to the development of SCLC treatment. The effects of Tanshinone IIA treatment on down-regulating SCLC proliferation were 4 points 8% in the current meta-analysis. Five articles that looked into the impact of Tanshinone IIA on down-regulating NSCLC proliferation were included in the meta-analysis in the second section of the study. A meta-analysis revealed that Tanshinone IIA treatment had a 6.2 percent down-regulation effect on NSCLC proliferation. Tanshinone IIA has been demonstrated in earlier research to possess antitumor properties and to be able to effectively suppress the growth of cell lines, including those from liver, pancreatic, and colon cancers.[16, 26] According to studies, Tanshinone IIA may inhibit HK2-mediated glycolysis in oral squamous cell carcinoma.[27] This could have an antitumor effect. Tanshinone IIA has been demonstrated in studies to potentially suppress HK2-mediated glycolysis in oral squamous cell carcinoma, which may have an antitumor effect. Additionally, Tanshinone IIA treatment decreases PKM2 and HK2 expression in cervical cancer cells.[28] On the other hand, not much research has been done in this field, and opinions differ on the findings. A study shows EMT links to the NSCLC and SCLC metastasis processes.[29] Epithelial cells alter their polarity from apical-basal to anterior-posterior during EMT, severing their connections with nearby cells and adjusting to the characteristics of migrating mesenchymal cells.[29] According to study findings, Tanshinone IIA may effectively contribute to tumor growth and cell migration by upregulating E-cadherin and downregulating vimentin expression.[29]

5. Conclusion

According to current research, tanshinone IIA can inhibit the growth of both SCLC and NSCLC. Therefore, Tanshinone IIA is a viable treatment option for both. Future research should focus more attention on the numerous pathway inhibition studies that have been reported. Toxicological investigations require more research.

Conflict of Interest

The authors declared that there is no conflict of interest.

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References

[1] Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemporary Oncology/Współczesna Onkologia. 2021;25(1):45-52. https://doi.org/10.5114/wo.2021.103829.

[2] Casal-Mouriño A, Ruano-Ravina A, Lorenzo-González M, Rodríguez-Martínez Á, Giraldo-Osorio A, Varela-Lema L, et al. Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. Translational Lung Cancer Research. 2021;10(1):506. https://doi.org/10.21037/tlcr.2020.03.40.

[3] Organization WH. Lung cancer: World Health Organization; 2023 [Available from: https://www.who.int/news-room/fact-sheets/detail/lung-cancer.

[4] Wéber A, Morgan E, Vignat J, Laversanne M, Pizzato M, Rumgay H, et al. Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040. BMJ open. 2023;13(5):e065303. https://doi.org/10.1136/bmjopen-2022-065303.

[5] Bade BC, Cruz CS. Lung cancer 2020: epidemiology, etiology, and prevention. Clinics in chest medicine. 2020;41(1):1-24. https://doi.org/10.1016/j.ccm.2019.10.001.

[6] Miller M, Hanna N. Advances in systemic therapy for non-small cell lung cancer. Bmj. 2021;375. https://doi.org/10.1136/bmj.n2363.

[7] Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nature Reviews Disease Primers. 2021;7(1):3. https://doi.org/10.1038/s41572-020-00235-0.

[8] Saltos A, Shafique M, Chiappori A. Update on the biology, management, and treatment of small cell lung cancer (SCLC). Frontiers in oncology. 2020;10:1074. https://doi.org/10.3389/fonc.2020.01074.

[9] Wang K, Chen Q, Shao Y, Yin S, Liu C, Liu Y, et al. Anticancer activities of TCM and their active components against tumor metastasis. Biomedicine & Pharmacotherapy. 2021;133:111044. https://doi.org/10.1016/j.biopha.2020.111044.

[10] Chen Y, Yu M, Liu Z, Zhang Y, Li Q, Yang G. Effects of traditional Chinese medicine combined with chemotherapy for extensive-stage small-cell lung cancer patients on improving oncologic survival: study protocol of a multicenter, randomized, single-blind, placebo-controlled trial. Trials. 2021;22:1-8. https://doi.org/10.1186/s13063-021-05407-1.

[11] Xu XQ, Deng WQ, Wang DY, Li M, Kou DL, Zhang PT. Chinese medicine treatment prolonged survival in small cell lung cancer patients: a clinical observation. Chinese journal of integrative medicine. 2021;27:496-501. https://doi.org/10.1007/s11655-020-3197-1.

[12] Zeng P, Li J, Chen Y, Zhang L. The structures and biological functions of polysaccharides from traditional Chinese herbs. Progress in molecular biology and translational science. 2019;163:423-44. https://doi.org/10.1016/bs.pmbts.2019.03.003.

[13] Zhu B, Zhang QL, Hua JW, Cheng WL, Qin LP. The traditional uses, phytochemistry, and pharmacology of Atractylodes macrocephala Koidz.: a review. Journal of Ethnopharmacology. 2018;226:143-67. https://doi.org/10.1016/j.jep.2018.08.023.

[14] Zhang W, Liu C, Li J, Lu Y, Li H, Zhuang J, et al. Tanshinone IIA: New perspective on the anti-tumor mechanism of A traditional natural medicine. The American Journal of Chinese Medicine. 2022;50(01):209-39. https://doi.org/10.1142/S0192415X22500070.

[15] Chen J, Bi Y, Chen L, Zhang Q, Xu L. Tanshinone IIA exerts neuroprotective effects on hippocampus-dependent cognitive impairments in diabetic rats by attenuating ER stress-induced apoptosis. Biomedicine & Pharmacotherapy. 2018;104:530-6. https://doi.org/10.1016/j.biopha.2018.05.040.

[16] Guo R, Li L, Su J, Li S, Duncan SE, Liu Z, et al. Pharmacological activity and mechanism of tanshinone IIA in related diseases. Drug Design, Development and Therapy. 2020:4735-48.

[17] Jiang Y, Bi Y, Zhou L, Zheng S, Jian T, Chen J. Tanshinone IIA inhibits proliferation and migration by downregulation of the PI3K/Akt pathway in small cell lung cancer cells. BMC Complementary Medicine and Therapies. 2024;24(1):68. https://doi.org/10.1186/s12906-024-04363-y.

[18] Qi H, Chen Z, Qin Y, Wang X, Zhang Z, Li Y. Tanshinone IIA inhibits cell growth by suppressing SIX1-induced aerobic glycolysis in non-small cell lung cancer cells. Oncology Letters. 2022;23(6):1-11. https://doi.org/10.3892/ol.2022.13304.

[19] Bai S, Cui S, Wen W, Leung EL, Bai J, Lin H, et al. Tanshinone IIA Suppresses Non-Small Cell Lung Cancer Through Beclin-1-Mediated Autophagic Apoptosis. Engineering. 2022;19:128-38. https://doi.org/10.1016/j.eng.2021.07.014.

[20] Gao F, Li M, Liu W, Li W. Inhibition of EGFR signaling and activation of mitochondrial apoptosis contribute to tanshinone IIA-mediated tumor suppression in non-small cell lung cancer cells. OncoTargets and therapy. 2020;13:2757-69.

[21] Xie J, Liu J, Liu H, Liang S, Lin M, Gu Y, et al. The antitumor effect of tanshinone IIA on anti-proliferation and decreasing VEGF/VEGFR2 expression on the human non-small cell lung cancer A549 cell line. Acta Pharmaceutica Sinica B. 2015;5(6):554-63. https://doi.org/10.1016/j.apsb.2015.07.008.

[22] Zhang J, Wang J, Jiang JY, Liu SD, Fu K, Liu HY. Tanshinone IIA induces cytochrome c-mediated caspase cascade apoptosis in A549 human lung cancer cells via the JNK pathway. International journal of oncology. 2014;45(2):683-90. https://doi.org/10.3892/ijo.2014.2471.

[23] Cheng CY, Su CC. Tanshinone IIA may inhibit the growth of small cell lung cancer H146 cells by up-regulating the Bax/Bcl-2 ratio and decreasing mitochondrial membrane potential. Molecular Medicine Reports. 2010;3(4):645-50. https://doi.org/10.3892/mmr_00000310.

[24] Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. Cancers. 2021;13(4):820. https://doi.org/10.3390/cancers13040820.

[25] Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. Journal of hematology & oncology. 2019;12. https://doi.org/10.1186/s13045-019-0736-3.

[26] Lin CY, Chang TW, Hsieh WH, Hung MC, Lin IH, Lai SC, et al. Simultaneous induction of apoptosis and necroptosis by Tanshinone IIA in human hepatocellular carcinoma HepG2 cells. Cell death discovery. 2016;2(1):16065. https://doi.org/10.1038/cddiscovery.2016.65.

[27] Li M, Gao F, Zhao Q, Zuo H, Liu W, Li W. Tanshinone IIA inhibits oral squamous cell carcinoma via reducing Akt-c-Myc signaling-mediated aerobic glycolysis. Cell Death & Disease. 2020;11(5):381. https://doi.org/10.1038/s41419-020-2579-9.

[28] Liu Z, Zhu W, Kong X, Chen X, Sun X, Zhang W, et al. Tanshinone IIA inhibits glucose metabolism leading to apoptosis in cervical cancer. Oncology Reports. 2019;42(5):1893-903. https://doi.org/10.3892/or.2019.7294.

[29] Xie S, Wu Z, Qi Y, Wu B, Zhu X. The metastasizing mechanisms of lung cancer: Recent advances and therapeutic challenges. Biomedicine & Pharmacotherapy. 2021;138:111450. https://doi.org/10.1016/j.biopha.2021.111450.

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