Targeting SQLE with ellagic acid and terbinafine: A low-cost, synergistic therapeutic strategy for bladder and lung cancer

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Bladder cancer (BCa) and non-small cell lung cancer (NSCLC) are among the most common and lethal malignancies worldwide, accounting for nearly 3 million new cases and over 1.5 million deaths annually.[1] For NSCLC, while targeted therapies (e.g., EGFR-TKIs) and immunotherapies (e.g., PD-1 inhibitors) have improved outcomes, primary and acquired resistance develops in most patients, and the high cost of these agents limits accessibility in resource-limited settings.[2] Therefore, there is an urgent need for affordable and effective therapeutic strategies for both malignancies.

Squalene epoxidase (SQLE), a key rate-limiting enzyme in the cholesterol biosynthesis pathway, has recently been identified as an oncogenic driver in multiple cancer types.[3] Analysis of clinical datasets from The Cancer Genome Atlas (TCGA) and our own patient cohorts revealed that SQLE is significantly upregulated in both BCa and NSCLC tumor tissues compared to adjacent normal tissues, with high SQLE expression correlating with poor overall survival (Figure 1A).[3] Functionally, SQLE overexpression promotes cancer cell proliferation, migration, and cell-cycle progression by activating cholesterol synthesis and inducing Reactive Oxygen Species (ROS) production, while SQLE knockdown suppresses these malignant phenotypes both *in vitro* and *in vivo*.

To validate the therapeutic potential of targeting SQLE, we first evaluated the anti-tumor efficacy of the SQLE inhibitor terbinafine in combination with the natural SQLE downregulator ellagic acid.[4-5] As shown in Figure 1B, the combined treatment of oral administration of ellagic acid (40 mg/kg/day) plus terbinafine (60 mg/kg/day) consistently delayed tumor growth over the treatment period and significantly reduced tumor weight compared to either monotherapy or vehicle controlin UMUC3 bladder cancer xenografts. Western blot analysis of tumor tissues confirmed that ellagic acid effectively abrogated the terbinafine-induced compensatory upregulation of SQLE protein expression (Figure 1C). These findings were consistently reproduced in A549 lung cancer xenografts, where the combination therapy again produced the greatest reduction in the tumor weight and effectively reversed the terbinafine-induced upregulation of SQLE (Figures 1D-E). Notably, the combination did not cause significant body weight loss in either model, indicating a favorable safety profile, and we have now explicitly noted in the revised manuscript that in-depth mechanistic and safety profiling will be essential in our future research. The enhanced anti-proliferative and anti-migratory effects were also observed in additional BCa cell lines (J82, RT112) and NSCLC cell lines (H460) *in vitro*, as assessed by MTT, colony formation and wound healing assays (Figures 1F-H).

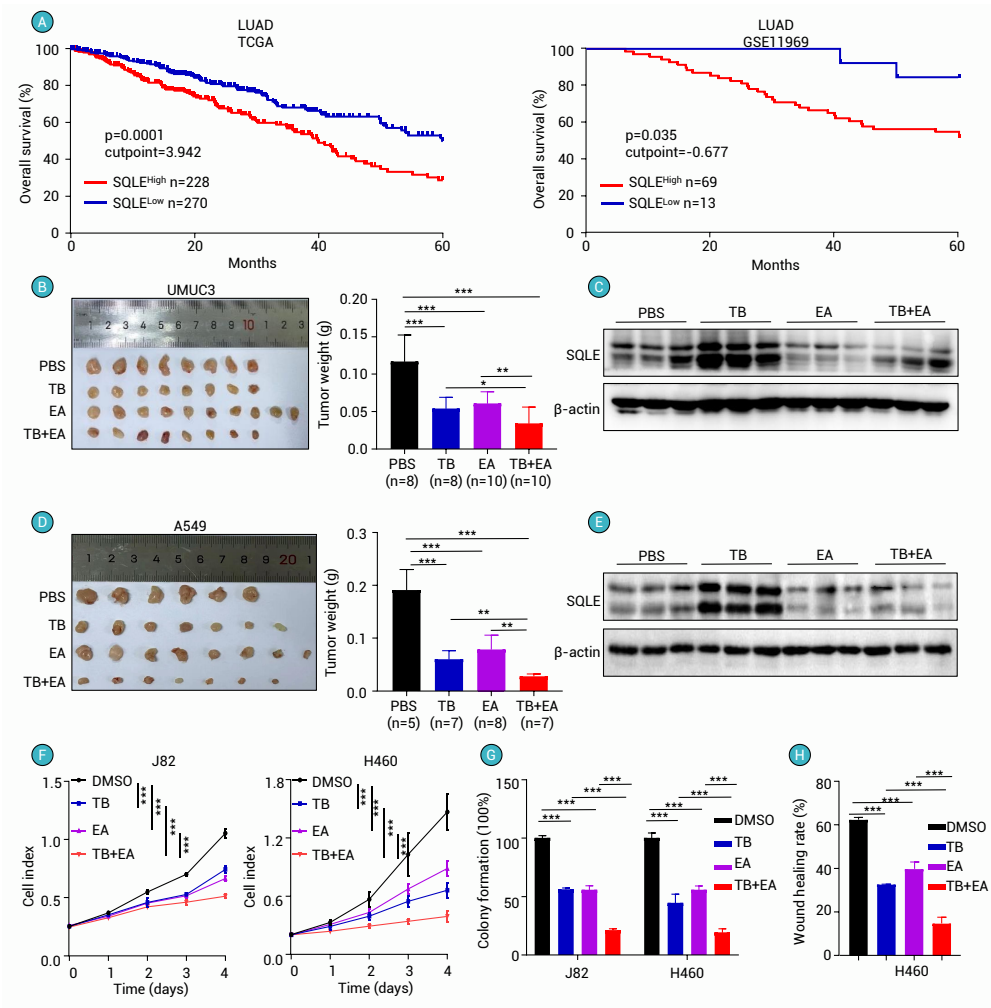

Figure 1. Terbinafine and ellagic acid enhance the suppression of bladder and lung xenograft growth and block compensatory SQLE upregulation (A) Kaplan-Meier curves showing the relationship between SQLE mRNA expression and overall survival in the TCGA cohort (left) and the GSE11969 cohort (right). (B) Tumor weight of UMUC3 (bladder) subcutaneous xenografts in Phosphate-Buffered Saline (PBS), terbinafine (TB), ellagic acid (EA), and terbinafine+ellagic acid (TB+EA) groups. (C) Western blot analysis of SQLE protein expression in UMUC3 xenograft tumors. (D) Tumor weight of A549 (lung) subcutaneous xenografts in control, TB, EA, and TB+EA groups. (E) Western blot analysis of SQLE protein expression in A549 xenograft tumors. (F-H) Effects of DMSO, TB, EA, and TB+EA combination treatment on cell proliferation (F), colony formation ability (G), and migration capacity (scratch assay, H). Data are mean ± SD. *p < 0.05, **p < 0.01, ***p < 0.001. Kaplan-Meier survival analysis (A). Unpaired, two-tailed Student's t-test (B, D, F, G, H).

SQLE overexpression drives tumor progression by enhancing cholesterol synthesis—a critical source of lipid membranes for rapidly dividing cells—and by inducing ROS production, which can promote genomic instability and survival signaling. Terbinafine, a well-known antifungal drug that inhibits fungal SQLE, also effectively inhibits human SQLE enzymatic activity and shows anti-tumor potential. However, as demonstrated in our studies, terbinafine monotherapy leads to compensatory upregulation of SQLE protein expression, likely through a cholesterol

homeostasis-dependent feedback response triggered by enzymatic inhibition.[4] This upregulation limits its long-term efficacy and may contribute to metabolic side effects. Ellagic acid, a natural polyphenol found in fruits such as pomegranates and berries, can downregulate SQLE expression at both the mRNA and protein levels,[5] but its dose-dependent cytotoxicity and poor systemic bioavailability restrict its use as monotherapy. To overcome these limitations, we developed a combination therapy comprising ellagic acid and terbinafine (mass ratio 4:7, optimal for both cancer types as determined by dose-response matrix assays). The key innovation is that ellagic acid suppresses the terbinafine-induced compensatory SQLE upregulation, thereby restoring the sensitivity of cancer cells to SQLE inhibition. This dual mechanism—direct enzymatic inhibition by terbinafine combined with transcriptional/translational suppression by ellagic acid—results in an enhanced anti-proliferative effect while allowing a lower dose of ellagic acid to reduce its toxicity. This invention has been granted Chinese patents for both bladder cancer (ZL 2025 1 1206078.3) and lung cancer (ZL 2025 1 1206044.4), as well as Hong Kong patents (40125789 B and 40125790 B).

Both terbinafine and ellagic acid are inexpensive and widely available. Terbinafine is a generic antifungal drug with a well-established safety profile, while ellagic acid is a natural compound that can be extracted from plant sources or chemically synthesized at low cost. The terbinafine and ellagic acid combination represents a substantially more affordable and widely available oral treatment strategy with potential suitability for outpatient use, particularly in resource-limited settings. Oral administration further reduces hospitalization and nursing costs while improving patient compliance, making this regimen suitable for outpatient and community-based treatment, particularly in primary hospitals where advanced infusion facilities may be unavailable.

Given that SQLE dysregulation has been observed in various malignancies such as hepatocellular carcinoma, prostate cancer, and colon cancer, this combination therapeutic approach could potentially be explored for these cancer types in future research. Preclinical studies in our laboratory are currently evaluating the efficacy of this combination therapy in additional tumor models. Furthermore, the combination can be formulated into a ready-to-use oral tablet or capsule using standard pharmaceutical excipients. With automated production and quality control, a low-cost generic formulation could be developed and widely distributed. In the future, this combination therapy could be combined with biomarker screening,such as assessing SQLE expression in tumor biopsies or circulating tumor cells, to identify patients most likely to benefit, thereby enabling a precision medicine approach even in low-resource settings.

In conclusion, the ellagic acid-terbinafine combination offers an enhanced, low-cost, and low-toxicity therapy for both bladder and lung cancer by targeting SQLE and blocking its compensatory upregulation. This invention exemplifies successful "old drug repurposing plus natural product synergy" across multiple cancer types. Given its affordability, oral availability, favorable safety profile, and strong preclinical validation, this combination has significant potential for clinical translation and popularization, particularly in regions where access to expensive targeted therapies and immunotherapies remains limited.

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DECLARATION OF INTERESTS

The authors declare no competing interests.